

Drug Safety

Cultural, Scientific, and Engineering Issues

N Stockbridge

Division of Cardiovascular and Renal
Products, CDER, FDA

Outline

Cardio-Renal is one of 16 new-drug review divisions in FDA/CDER, responsible for monitoring and fostering drug development throughout the life cycle, from first-in-man to post-marketing.

- **Culture**
- Science
- Engineering

Culture

- Our attitudes about safety affect its evaluation and interpretation.
 - **Primum non nocere (origins obscure)**
 - “First do no harm”
 - Try not to make things worse than they already are

Culture

- Our attitudes about safety affect its evaluation and interpretation.
 - Primum non nocere (origins obscure)
 - “First do no harm”
 - Try not to make things worse than they already are
 - **History of drug regulation – Safety First!**

Drug regulation: A brief history

- 1848 Drug Importation Act
- 1902 Biologics Control Act
- 1906 Food and Drug Act
 - [FDA] has to prove adulteration or misbranding
- 1938 Food, Drug and Cosmetic Act
 - Sponsor to prove safety
- 1962 Kefauver-Harris Amendments
 - Sponsor to prove effectiveness



- 2008 FDA initiative in response to PDUFA
- Targeting post-marketing safety surveillance
- New drug review divisions get a dedicated deputy director for safety
- Formal business process for safety review mirroring that for NDA review
- Office of Surveillance and Epidemiology
 - Office of Pharmacovigilance and Epidemiology
 - Office of Medication Error Prevention and Risk Management
 - Now ~half the size of the review divisions

Culture

- Our attitudes about safety affect its evaluation and interpretation.
 - Primum non nocere (origins obscure)
 - “First do no harm”
 - Try not to make things worse than they already are
 - History of drug regulation – Safety First!
 - **Sainthood**

FDA's most famous reviewer



Frances Kelsey receives President's Award for Distinguished Federal Civilian Service for review that prevented approval of thalidomide until further studies were performed.

But...

Testing she sought had nothing to do with thalidomide's teratogenicity.

Culture

- Our attitudes about safety make its evaluation and interpretation more difficult than it ought to be.
 - Primum non nocere (origins obscure)
 - History of drug regulation – Safety First!
 - Sainthood
 - **Risk aversion in practice today**
 - Firestorm of controversy around approval of only the higher dose of dabigatran when it caused about the same amount of bleeding and prevented more strokes than did warfarin

Outline

- Culture
- Science
 - **Pre-approval**
 - Post-approval
- Engineering

Study-based data

- Denominators
- Protocol-driven data collection
 - Timing
 - Analytes
 - Event characterization
- Replication
 - Studies
 - Doses

Study-based data and tools

- Analysis datasets to support primary analysis began being reviewed in the 1980s
- Beginning around 1990, we began getting comprehensive study data at the time of application for marketing approval.
- Initial access was through stand-alone systems with limited functionality (and few reviewers knew what questions might interest them).
- By late 1990s to mid-2000s,
 - More data
 - More data management experience
 - Better in-house training on general-purpose statistical tools (but not principles of multiplicity)

Pre-approval statistical framework

- Efficacy is usually assessed within a fairly structured statistical framework, so it is possible to say something about the false positive rate.
- Safety is seldom assessed with appreciation for multiplicity. There are many safety measures, any one of which, trending adversely, can be cause for concern.

Things will get worse before they get better

- Damage is limited because although data exist, there are few reviewers with data management skills necessary to cause trouble.
- That barrier is decreasing...
 - CDISC data standards
 - JANUS clinical trials data warehouse
 - Data-model-aware review tools
 - Education in use of tools
- No *discipline* around analyses

Warning on Empirica Study ...is not enough

- **The results are to be used for exploratory analysis.**
- **Consult your statistician about interpreting potential signals.**
- **No regulatory decisions should be made based solely on the results of the software analysis.**

Is science possible in pre-market evaluation of safety?

- Are there corresponding non-clinical and clinical findings (mechanism)?
- Is there a syndrome here?

- Yes, a role for judgment (exercised to varying degrees)
- But nothing like an algorithm that allows you cover for dismissing an implausible finding

Outline

- Culture
- Science
 - Pre-approval
 - **Post-approval**
- Engineering

Post-approval data sources

- **FDA Adverse Event Reporting System (FAERS)**
- Sentinel
- Meta-analyses

FDA Adverse Events Reporting System

- Data spontaneously and poorly reported, from uncertain denominator, at a rate dependent on time, media
- Historically, queries stimulated by clinical reviewer insights and memory
- Empirica Signal (Lincoln → Oracle; early 2000s) allowed disproportionality scoring

Division's FAERS data ca. 2006

- Over 172,000 distinct drug-event pairs
- Top signal: Hyperphosphatemia with Sevelamer score 381 (95% CI 322-448)
- 24 drug-event pairs with lower bound >100
- 1000 drug-event pairs with lower bound >10

FDA Adverse Events Reporting System

- Data spontaneously and poorly reported, from uncertain denominator, rate dependent on time, media
- Historically, queries stimulated by clinical reviewer insights and memory
- Empirica Signal (Lincoln → Oracle; early 2000's) allowed disproportionality scoring
- **By 2004, we were incapacitated by internally generated “safety signals”, with no plan how to allocate resources.**
- **We developed a comprehensive strategy to look for worst signals and manage them, layering on a system to annotate signals, and got it incorporated in Empirica Signal.**
- **We underwent an about 18-month process to annotate apparent signals in the Division's portfolio. A few other review divisions followed.**
- **Data → Tools → Chaos → Discipline**

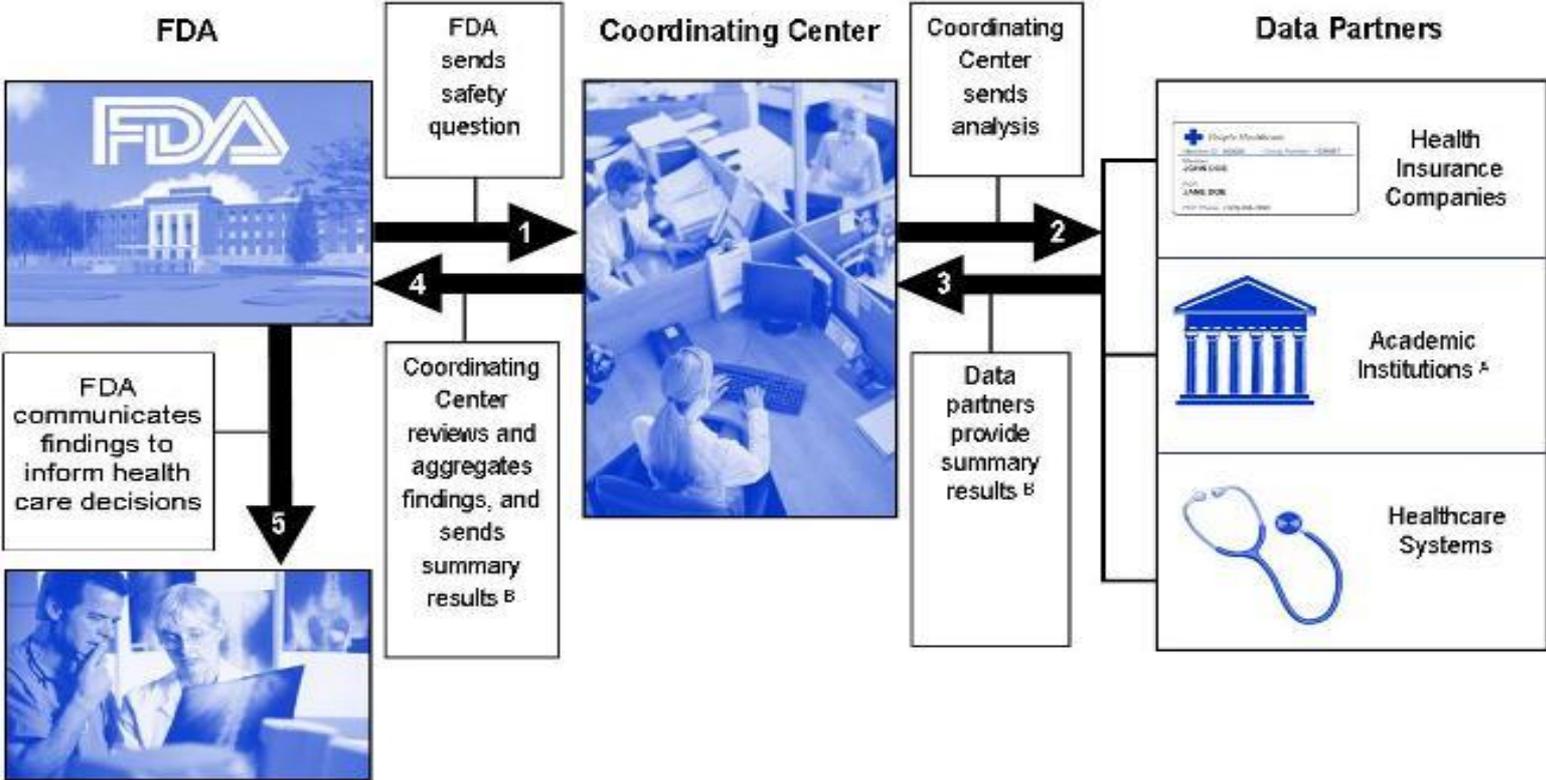
Post-approval data sources

- FDA Adverse Event Reporting System (FAERS)
- **Sentinel**
- Meta-analyses

“Mini-”Sentinel pilot

- www.mini-sentinel.org
- Insurer-, claims-based
 - Aetna
 - Kaiser-Permanente
 - Harvard Pilgrim Health
 - ...
- Enrollment (31 December 2012)
 - 130 M individuals (41 M active)
 - 382 M person-years

Figure 1: Overview of the Mini-Sentinel Safety Question Evaluation Process



- A. Only those academic institutions with electronic healthcare data will receive safety questions for evaluation.
- B. Data partners will provide summary results from analyses conducted within their secure data environments. Those summary results will not include directly identifiable health information.

Dabigatran for AF

- Approved 2010 based on RE-LY trial
 - N=18113, 2-year follow-up
 - Compared with warfarin
 - Better stroke prevention (35% decrease)
 - Similar numbers of ischemic and hemorrhagic strokes prevented
 - Similar or somewhat less bleeding risk
- Post-approval
 - >10000 post-marketing reports of bleeding events, 100 deaths in first year
 - Much higher rate than with warfarin

Dabigatran vs warfarin in Sentinel

- Among new users...
 - GIB: D 1.6 vs W 3.2 /100000 patient-days
 - ICH: D 0.8 vs W 2.4 /100000 patient-days
- Second round underway looking at D vs W among any users (Sentinel and CMS)
 - Rates look more similar to RE-LY (but certainly not higher on D than on W)

Sentinel Implications

- Partners responsible for privacy concerns of their own data
- Number of queries per year is very limited
 - Forces prioritization, limits noise
 - Won't support surveillance, data-determined prioritization

Alternative to Sentinel?

- Electronic medical record data
- Known denominators
- Unrestricted queryable
- Basis for
 - Registries (customized data collection)
 - Trial recruitment
 - Active surveillance

Post-approval data sources

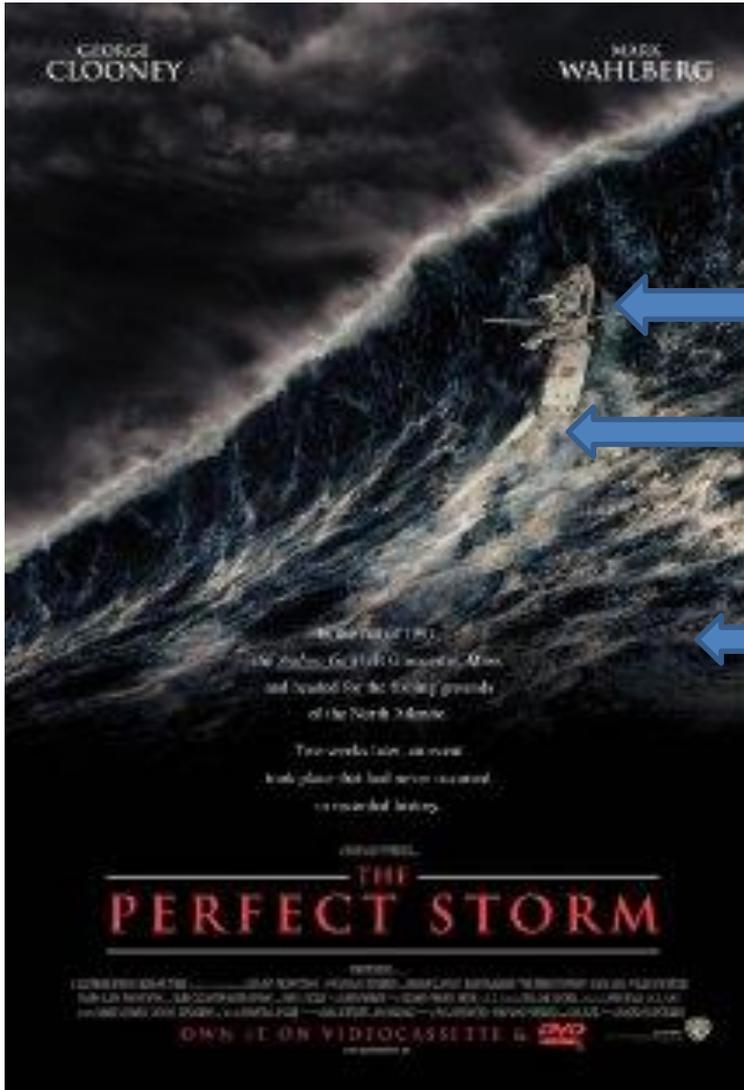
- FDA Adverse Event Reporting System (FAERS)
- Sentinel
- **Meta-analyses**

Meta-analyses: ARBs and cancer

- Sipahi et al. (2010) Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomized controlled trials. *Lancet Oncol* 11(7):627-636.
- Nissen SE. (2010) Angiotensin-receptor blockers and cancer: urgent regulatory review needed. *Lancet Oncol* 11(7):605-606.

ARBs do not cause cancer

- 8% nominal increase
- Stimulated by trend in one study; included in meta-analysis
- No mechanistic basis
- Refuted by several more comprehensive meta-analyses (one FDA, two others), ruling out as much as the original point estimate
- Comprehensive review of non-clinical carcinogenicity data—ARBs appear to be neutral or better
- HUGE expenditure of resources; unsatisfactory to reject on methodological basis



Missense of purpose



Cheap, efficient tool



Data

Evolution of safety science

	Data	Tool	Chaos	Discipline
FAERS		✓	✓	✓
Sentinel				
Premarket data		½ ✓	½ ✓	
Meta-analysis			½ ✓	

Outline

- Culture
- Science
- **Engineering**
 - Are there safety problems that are well enough understood that you can design assays to evaluate them?

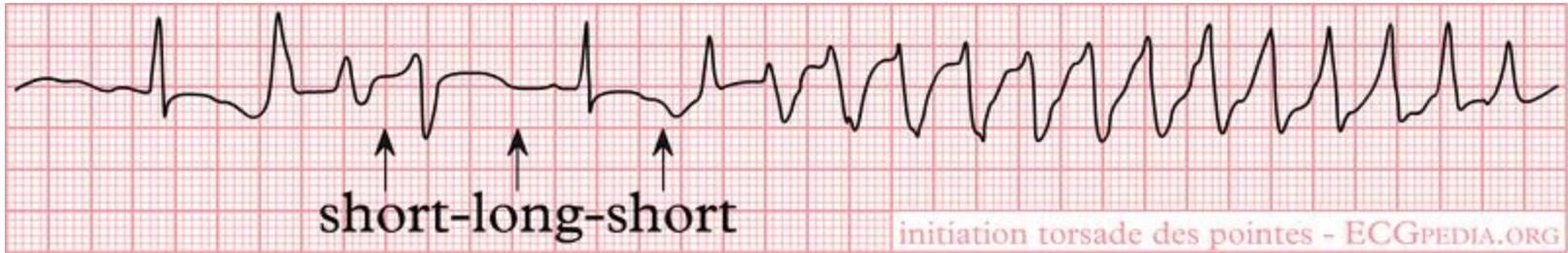
Drugs Removed From Market for Arrhythmia Risk

- 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

(Twisting of the points)



Responses to TdP crisis

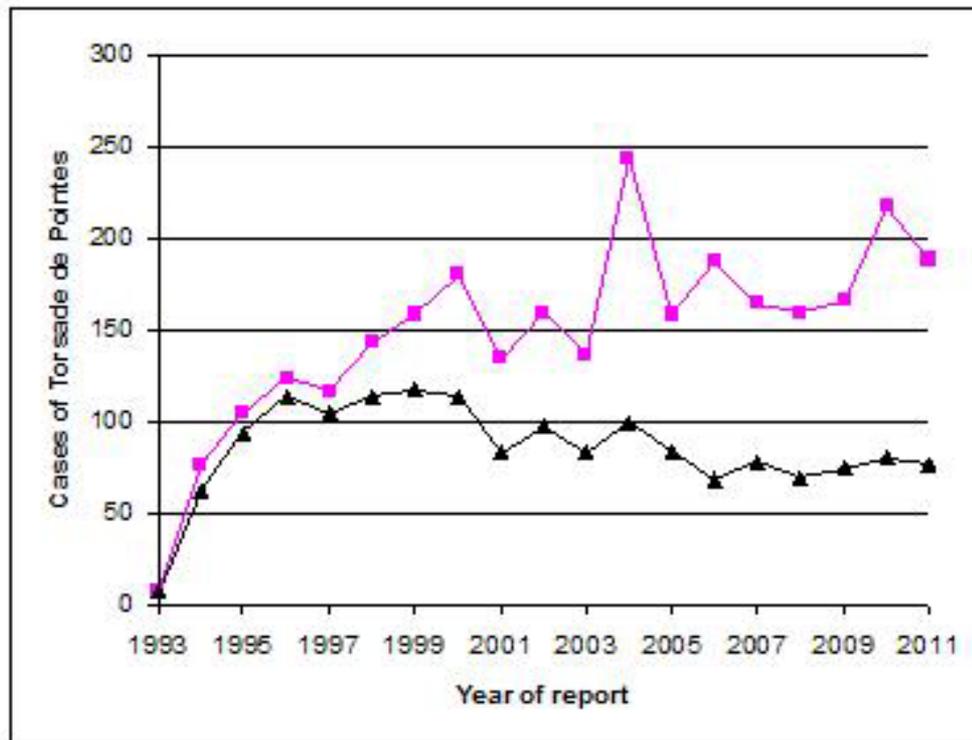
- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

Direct costs

- Since 2005
 - Around 300 studies TQT studies reported to FDA
 - Estimated 450 TQT studies performed
 - Estimated cost per study is few \$M
- 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

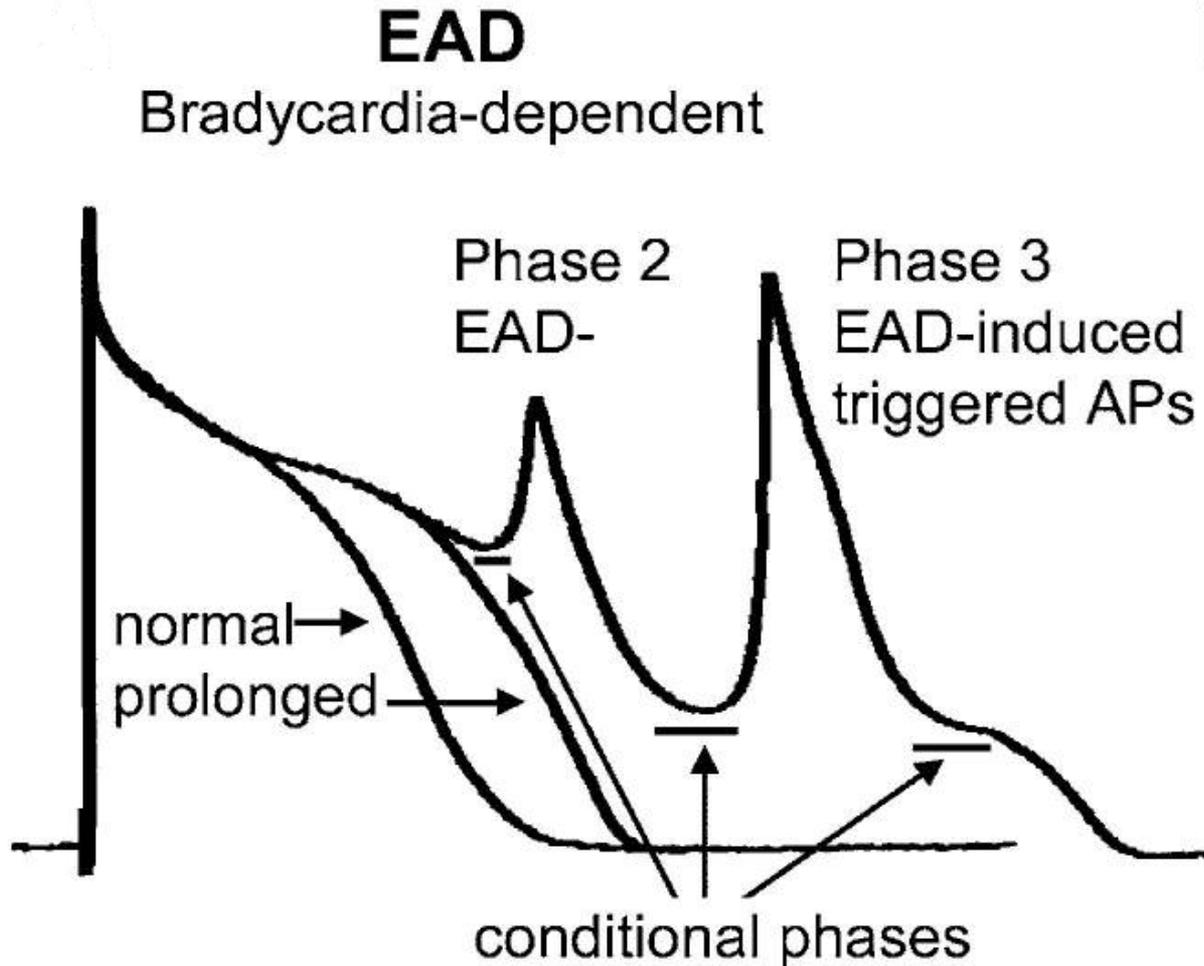
Success? I think not...

- 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 can be a bad bargain**
 - Reduced affinity for target receptor
 - New off-target effects
 - No drug candidate

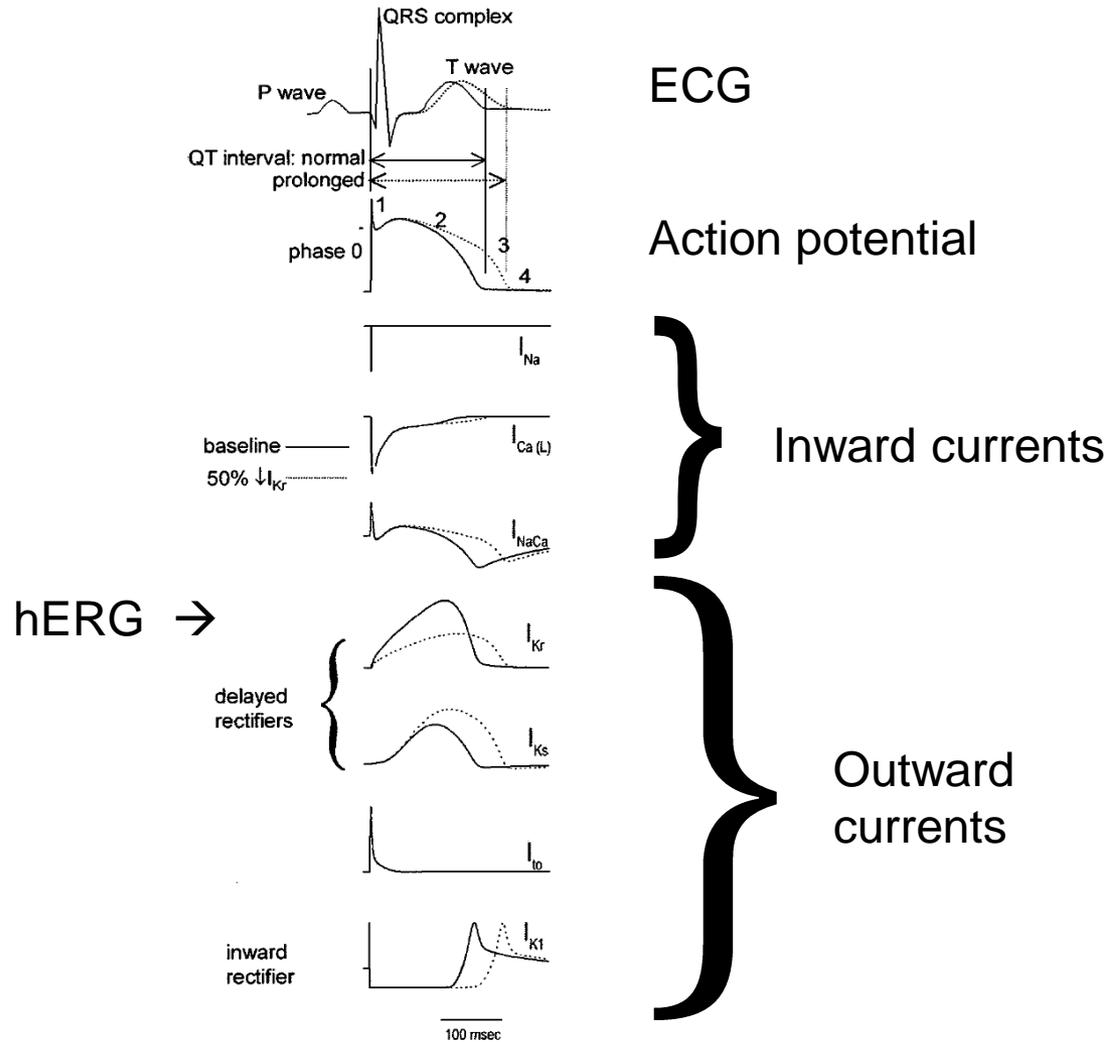
We can do better

- Basis of TdP-like arrhythmias pretty well understood
 - Vulnerability during repolarization
 - Heterogeneity in electrical state across the heart
 - Contributors include disease, non-uniform drug or electrolytes
 - Rare event—you can go decades without an arrhythmia

Vulnerability during repolarization



Cardiac ionic currents



Multiple ion channel effects matter

- Because hERG effects are dramatic, it used to be thought that hERG was especially poorly designed for the pharmacologist, but now other ion channels are known to be fairly often the target—or one of the targets—for small molecule drugs.
- These other ion channel effects can make matters worse or better
 - Need relatively intact inward current to generate an EAD, so verapamil and ranolazine (both hERG blockers plus) are antiarrhythmic

Ways to improve proarrhythmia detection pre-clinically

- Classic pharmacology
 - Cells/tissue/organ + every drug → discriminant metric
 - Lots of work ongoing in this vein
- Mechanistic approach
 - Study drug effects on all/major ion channel types
 - Reconstruct the drug effect on cardiac action potential
 - Assess the vulnerability throughout the repolarization phase, at various rates, etc.

Mechanistic proarrhythmia assay

- Building upon work at Lilly, AbbVie, AstraZeneca, ChanTest etc.
- Engaging industry/academia/regulators through ILSI-HESI, Safety Pharmacology Society, and Cardiac Safety Research Consortium
- Engineering work is ongoing; testing/calibration in a year
- Goal of better labeling, more safe drugs in development

Summary

Our goal for drug development ought to be optimization of net benefit, not absolute reduction of risks. Regulators (at least) ought not be practicing “defensive medicine”.

There is little science (discipline, statistical rigor) in safety evaluation. Consequences of this will worsen as more data and better tools become available.