Balancing risk and benefit in drug development

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A regulator's view of the industry perspective

- Probably rationally subject to economic decision-making
  - Cost of drug development
  - Chances of success
  - How big the patient population is
  - What you can charge for drug

A regulator’s view of the regulatory perspective

- A rational approach is not possible
- The heuristic isn’t too bad
- We ought not be afraid to tinker further

A rational approach is not possible

- Problem being addressed:
  - Weighing the benefits of treatment against adverse effects
  - Involves value judgments
- Benefits defined by effects on how someone
  - Feels
  - Functions
  - Survives
  - Or surrogates with an established relationship to clinical benefit
- Safety
  - Off-target effects
  - Exaggerated on-target effects
  - What you don’t know

Problem 1

- Benefits
  - Assessed in the context of formal hypothesis testing
  - Results in estimated effect size and confidence limits, interpretable in terms of how likely the findings are to be reproducible
- Adverse effects
  - Scan using “all tests reasonably applicable”
    - Non-clinical toxicology, reproductive toxicology, carcinogenicity
    - Labs, vital signs, physical exam, ECGs, and other routine monitoring
    - Adverse events—solicited and spontaneously reported
  - No conceivable correction for multiplicity
  - Even ignoring multiplicity, no power to observe rare events clinically

Comparing benefits and risks—part 1

Benefits	Risks

Problem 2

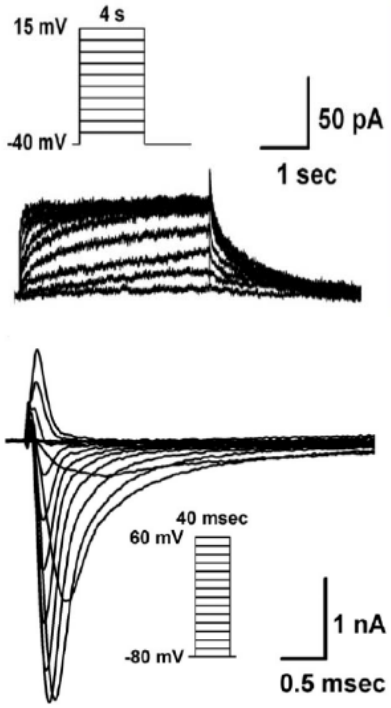
- Emphasis on safety / risk aversion
  - History
    - 1848 Drug Importation Act
    - 1906 Food and Drug Act
    - …
    - 1962 Keyfauver-Harris Amendments
  - 2008 Safety First Initiative
    - Office of Surveillance and Epidemiology n=224
    - 16 New Drug Review Divisions
      - Deputy Director for Safety
      - Dedicated Regulatory Project Manager
      - Safety issue tracking, processes similar to NDAs

Risk aversion and decisions

- Anticoagulation for atrial fibrillation
  - Dabigatran—110 and 150 mg
    - 110 mg: Fewer major bleeds and about same stroke reduction as warfarin
    - 150 mg: About the same major bleeding risk and fewer strokes than warfarin
- Thorough QT studies
  - Existing paradigm eliminated drug withdrawals for TdP risk
  - High sensitivity came with low specificity
    - Dropping good compounds from development
    - Labeling of risk where there is none

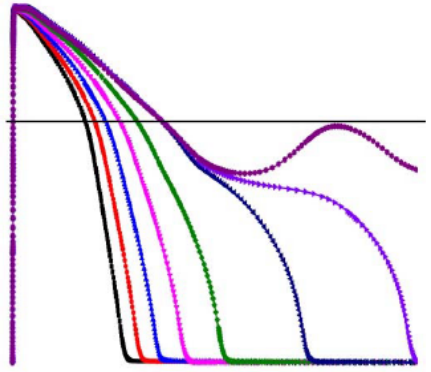
Components of the Comprehensive Proarrhythmia In Vitro Assay (CiPA)

Drug Effects on Multiple Human Cardiac Currents

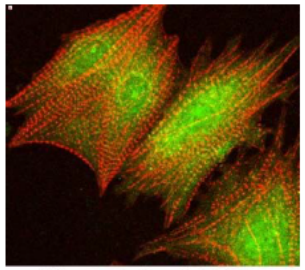


In Silico Reconstruction Cellular Human Ventricular Electrophysiology

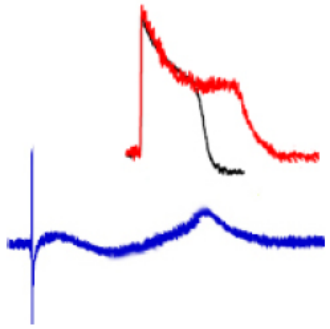
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



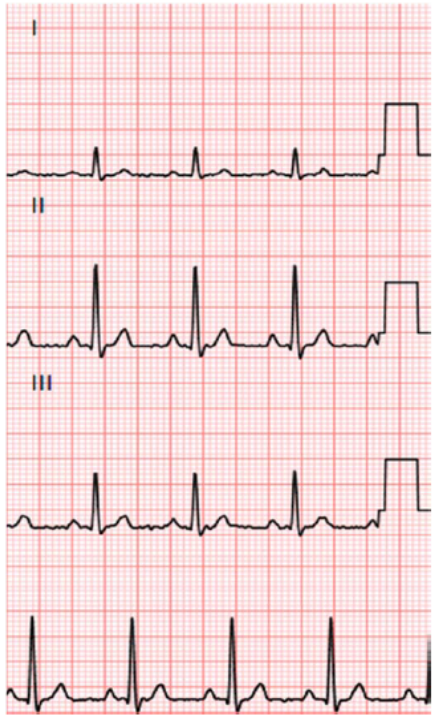
In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes



McEwen Cntr for Regen Med., Toronto



Clinical Evaluation Unanticipated Electrophysiology



Heuristic

- EMA model – Voting to integrate various value systems
- US model – Authority down-delegated to one person
  - Internal
    - Highly interactive review teams
    - Equal Voice
  - External
    - Advisory Committees
    - Citizen's Petitions
    - Patient engagement programs
    - Participation in consortia and meetings (like this one)
- International
  - Periodic teleconferences FDA-EMA-HC by therapeutic area
  - Joint EMA-FDA meetings with sponsors
  - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
    - US, EMA, Japan; expanding to Canada, Switzerland, others
    - Guidance on consensus topics
      - Reduce interface differences
      - Principles of evaluation

Outputs in EMA vs FDA

- Decisions usually similar
- Time frames for decisions are similar
- Main barrier tends to be related to effectiveness, not safety

What is success?

- A measure might be the fraction of the time you pull a drug off the market.
  - Some drugs do come off the market, but it is difficult to say how many of these are purely for business reasons and how many decisions were patently for safety-related problems. Of those that are safety-related, some reflect appearance in the marketplace of drugs that are safer; these don't reflect bad decisions, but evolution.
  - The optimum proportion of drugs to fail in the marketplace is not zero; that would likely mean the bar was too high and that some good products weren't making the grade. In a recent discussion of drugs to treat orphan diseases, a highly placed CDER official suggested the post-marketing failure rate might appropriately be 20%, taking into consideration failures related to effectiveness.

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- Can’t be done
- Have to do it anyway
- Even decades after the last major allocation of responsibilities, basic philosophical principles remain subject of active debate and evolution