Balancing risk and benefit in drug development

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FDA
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

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>![Target with dart]</td>
<td>![Dartboard with broken dart]</td>
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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**
  - Graph showing voltage and current relationships.
  - Mathematical equation: $I_{stim} = C \frac{dV_m}{dt} + I_m$

- **In Silico Reconstruction Cellular Human Ventricular Electrophysiology**
  - Graphs showing voltage and current changes over time.

- **In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes**
  - Image of cultured cells.

- **Clinical Evaluation Unanticipated Electrophysiology**
  - Graphs showing ECG recordings.
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