Clinical Forecasting in Drug Development

Asher Schachter, MD, MMSc, MS
Children's Hospital Informatics Program at Harvard-MIT
Division of Health Sciences and Technology
http://www.chip.org/
Division of Nephrology, Children's Hospital Boston
Harvard Medical School

Overview

• Drug development: the costs of failure

• Prototype model for pre-phase III data:
  – General approach
  – Evaluation, performance
  – Economic impact
  – Pediatric impact

• Pre-Clinical Modeling and Phase IV

New Chemical Entity (NCE)

• Preclinical: in vitro, in vivo
• IND, patent clock starts
• Phase I: $10-15 million
• Phase II: $25-35 million
• Phase III: $50-250 million
• NDA
• Phase IV

Drug Development

• TCSDD 2003: $897,000,000
• 70-90% of INDs fail
• >60% of terminations: Phases II and III
• 2002: NDA approvals hit a 5-year low
• Combinatorial chemistry
• High-throughput screening

Primary Causes of Failure:
348 Terminated NCEs

Fail early, fail often

vs.

Stifling innovation

General Approach

• Populations of compounds

\[ P(\text{drug}, \text{success} \mid \text{prior attempts}) \]

• Prior attempts: “failures” and successes

Data: Two Domains

• New compound: Proprietary
  Summary statistics vs. Elemental data
  Preclinical data only (proprietary or not)

• Prior data: Ex-proprietary
  Publicly available vs. Company-specific
  Industry-wide data
de-identified

“GIGO”

Compound of Interest

• \( P(\text{safety}) \)
  Therapeutic indices specific to:
  • Organs: vital, disease-related
  • Toxicity metrics: \( \text{Cr} \) vs. \( \text{HTN} \) vs. proteinuria

• Efficacy: indication specific signals
  – in vitro
  – in vivo
  – humans

Prior Data

• Same mechanism as index compound
• Same indication as index compound
• All outcomes:
  – NDA approval + market success
  – NDA approval + later warnings
  – NDA not approved
  – Terminated prior to NDA submission

Prototype Bayes Net Topology

Economic Impact

• Phase III go/no-go: low-hanging fruit
  – Mean: \$283,000,000 per approved drug
  – Mean: \$160,000,000 per phase III trial

• Lead compound prioritization: upstream
  – Identified targets
  – Lead compounds

Economic Impact


Limitations

- Requires proprietary Phase I/II data
- Study subjects exposed to new drug

Preclinical Predictors of Phase IV

Pre-Clinical Modeling

- Global metrics that predict safety/efficacy in humans
  - Pre-clinical metrics (animals + in vitro)
  - Independent of drug class, action, or mechanism
- ALL DRUGS ARE POISONS:
  - Primary effect: desirable
  - Side effect: undesirable
- Safety and efficacy
  - Pharma: often disconnect safety ↔ efficacy
  - Therapeutic index: MTD/MEO
  - Safety and efficacy are tightly correlated VIA DOSE
Pre-Clinical Modeling: Rationale

- Every drug has a set of effects: desired (intended) effects versus undesired (unintended) effects, i.e., side effects.
- The distinction between desired and undesired effects is arbitrary.
- In the preclinical phase, the desired effects are known, while most if not all of the specific, unintended, undesirable side effects (toxicities) are unknown.
- Hypothesis: Drugs have unique sets of preclinical dose vs. effect curves that may or may not be specific to the different types of the drug's effects.
- Subtle quantifiable features of these curves are common between a given drug's desired effects and undesired (toxic) effects.
- Models that use these shared quantifiable features of dose-versus-desirable effect curves may predict tendencies for undesirable, unknown forms of non-idiosyncratic toxicity.

Methodology 1

- PubMed search for relevant preclinical publications
- Batch download: QUOSA
- Manual review:
  - Primary indication
  - No drug combinations
  - Minimum 3 doses (including control/placebo)
- Extract figures as jpegs, & tables as csv
  - Datathief: jpegs → csv

Figure D1. Overview of Specific Aims. RDC=receiver operator characteristic curve.

Methodology 2

- Import data into Preclinical Dose-Effect Repository (PreDER)
- Normalization

Methodology 3

- Metric calculations (336 total) on each dose-effect curve for each drug in PreDER
- For each metric: Summary metric for all of a given drug's dose-effect curves:
  - Drugs have variable number of curves
  - Model using each drug as a single case, not each experiment (dose-effect curve)
At This Point:

- Data Table:
  - Column 1: drugs
  - Columns 2-3: drug fate categories
  - Columns 4-340: summary metrics

Methodology:

- LOO cross validation
  - For each left out drug:
    - Train on remaining drugs: SVM, boosting
    - Test on left out drug
  - AUROC, accuracy, PPV, NPV

Results To Date:

- Phase IV: withdrawn vs. not withdrawn
- Drug interaction mechanisms: CYP450 inducer vs. inhibitor
- Cancer: project terminated vs. FDA-approved

Preclinical Prediction of Phase IV Events:

- ~70 drugs withdrawn from market since the 1960s: data obtainable for 56 of these drugs
- 55 drugs matching mechanism, remaining on market ≥ 2 years
- 4397 dose-effect curves extracted from 823 publications

In comparison to randomly permuted dataset:

- AUROC: 0.54
- Accuracy: 0.58
- PPV: 0.60
- NPV: 0.57

Preclinical Prediction of Drug Interaction Mechanistic Activities:

- 10 drugs: known CYP450 inducers
- 10 drugs: known CYP450 inhibitors
- 699 dose-effect curves extracted from 154 publications
Preclinical Prediction of Drug Interaction Mechanistic Activities

• 519 dose-effect curves extracted from 126 publications

Preclinical Prediction of Cancer Drug Termination/FDA Approval

• 24 antineoplastic drugs: development program terminated
• 10 antineoplastic drugs: FDA approved
• 519 dose-effect curves extracted from 126 publications

Summary

• Open source drug safety sentinel system that is based solely on preclinical data
  – Reduced exposure to unsafe drugs
  – Sentinel for potentially suppressed safety data
  – Reduced burden on post-approval surveillance systems
  – More robust pipelines
  – Investor confidence: Enable market forecasts
  – Reduced burden on regulators
  – Reduced burden on 3rd party payors