A Health Outcomes Approach to the Pre-Marketing Quantitative Risk-Benefit Modeling of New Pharmaceuticals

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Hypothesis

The outcomes research tools of:

- integrative modeling of long-term health outcomes and
- utility measurement

--could provide a useful methodology for a more formal, explicit, transparent, and quantitative process of assessing benefit-risk balance in each of the various stages of drug development and marketing, but focusing here on pre-marketing approval.
Outline of Presentation

• Brief Thought Experiment: Complexity of Information for Pre-Marketing Approval
• FDA Risk Guidances—The Role of Benefits
• Use of Health Outcomes Models and Quality-Adjusted Life Year (QALY) Metric from Outcomes Research
• Challenges, Recommendations, and Unresolved Issues
Background and General Caveats

• Three general types of economic evaluation:
  » Cost-Effectiveness Analysis (CEA)—Outcomes measured in clinical terms
  » Cost-Utility Analysis (CUA)—Outcomes measured as QALYs
  » Cost-Benefit Analysis (CBA)—Outcomes measured in monetary terms.

• Key caveats:
  » Focus here is on the “utility” part of CUA.
  » Not talking about measuring “costs” or doing CBA.
    • Product price is not an appropriate factor for the FDA to consider.
A Hypothetical Example: Pre-Approval Review of New Drug

• Product profile:
  » First-in-class anti-obesity product vs. low-calorie diet
  » Had over 8,000 patients in the two Phase III trials.
  » Trials showed mean weight reduction of 10 kg on average at 1 year with no independent effects on LDL, HBA1c, or BP. By end of year 2, mean loss was 8 kg vs controls.
  » Found 4 sudden cardiac deaths in experimental arm; 2 in the control arm in the two trials.
  » Have no plausible biological mechanism for any cardiac impact.
  » Other nuisance side effects: 4% with mild, transitory nausea and diarrhea.
Company’s Presentation to FDA

- Emphasizes:
  - Obesity is a major public health problem and that most alternative therapies aren’t particularly effective (present data on prevalence of obesity and its increase over time)
  - The observed nausea and diarrhea are mild and transitory, responsive to temporary dose reduction.
  - Strong, consistent efficacy results in two trials.
  - No significant drug-drug interactions
  - Summarizes long term epidemiologic evidence of the impact of obesity on co-morbidities and survival.
  - Rate of sudden cardiac death is not statistically different between the two arms, and observed rates are consistent with background rates in general population.
How would one characterize this information and process of weighing it?

- Piecemeal—non-integrated mix of many quantitative and qualitative pieces
- Expect different subjective, unobservable weights for different reviewers on the various pieces of evidence.
- Potential biases in interpreting low probability side effects (a la Kahneman & Tversky)
- Implicit framework for synthesizing the information
- No estimate of the health effects of delaying approval to gather more information
How does Advisory Panel and/or FDA decide whether to recommend/approve?

• Issue:
  » Benefits side looks good, but nagging concern about cardiac adverse events.
  » Should we gather more data on cardiac deaths before approval or via post-marketing surveillance after approval?

• How to weigh the pros and cons of delaying approval to gather more data?
Implicit Bioclinical Health Outcomes Model: The Benefits Side

Weight Loss

Long-Term Improvements in Surrogate Co-Morbidities:
- Glucose tolerance
- Cholesterol
- Blood Pressure

Improved Clinical Outcomes:
- Cardiovascular/Cerebrovascular Events

Better Health Outcomes:
- Length of Life
- Quality of Life
Basic Issues

• Drug approval is about balancing safety and efficacy, not about guaranteeing safety.

• Why? Too costly to get perfect safety measurement or effectiveness. Regulatory processes reflect this.

• FDA regulators are subject to countervailing forces:
  » Close working relationship with those they regulate could lead to bias.
  » Public visibility of some types of mistakes could bias decisions to minimize risk, rather than making the right balance.

• Why?
  » Approving an unsafe drug—a visible error
  » Keeping a beneficial drug off the market—a mostly invisible error

• What can be done to help find the right balance?
What do the guidances say about measuring benefit and benefit-risk balance?

- “Because different products pose different benefit-risk considerations . . ., it impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic safety study should be initiated. . .” (PV guidance)

- A major difficulty in relating benefits and risks is that they are measured in different units. Thus, one often needs to compare a modest benefit that occurs in many patients with a rare but very serious adverse effect. Benefits as well as risks are also patient specific and are influenced by such factors as the severity of the disease. . . . Thus, assessment and comparison of a product’s benefits and risks is a complicated process that is influenced by a wide range of individualized factors” (Emphasis added). RiskMAP DRAFT guidance)
How have health technology assessment (HTA) and health outcomes researchers dealt with this?

- **US Panel on Cost-Effectiveness in Health and Medicine:**
  
  » “For a Reference Case analysis, incorporation of morbidity and mortality consequences into a single measure should be accomplished using QALYs.”

- **National Institute of Clinical Excellence (NICE-UK)**

  » For the reference case, cost-effectiveness analysis is the appropriate form of economic evaluation. . . . Health effect should be expressed in quality-adjusted life years (QALYs).
Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation (Jan. 2006)

• “CEA, like BCA, offers a useful tool for the development and assessment of regulatory interventions to promote better health and safety. . . “

• “Recommendation 1: Regulatory CEAs that integrate morbidity and mortality impacts in a single effectiveness measure should use the **quality-adjusted life year** to represent net health effects.”
Could utility analysis (i.e., QALYs) be the common metric for the risk-benefit analysis?

- For most new drugs, estimating QALYs is going to require modeling, i.e., a framework for synthesizing information and extrapolating beyond what is traditionally collected in Phase III trials.

- **Pros:**
  - Pragmatic method that is already being applied across a wide spectrum of diseases, usually for purposes of reimbursement
  - Can be done at all stages of development
  - Gaining a wider audience

- **Cons:**
  - FDA and physicians don’t understand it or believe it is scientifically valid
  - Usually applied more to benefits than adverse events.
  - QALYs are risk neutral: How to include differences in risk preferences?
Incremental Net Health Benefit (INHB) of New Drug (2) vs. Current Therapy (1)

\[ \text{INHB} = (E_2 - E_1) - (R_2 - R_1) \]

where

\( \Rightarrow \) Effectiveness E is measured in QALYs
\( \Rightarrow \) Risk R is measured in QALYs

\((E_2 - E_1) > (R_2 - R_1) \uparrow \) Favorable benefit-risk balance

These measures are uncertain and would have distributions/variances around them\(\uparrow\)

1) Need to adjust them for risk aversion—e.g., use certainty equivalents.
2) Need to use probabilistic sensitivity analysis
Key Challenges in Evaluating Risks

1. Measuring **known** or potential side effects (adverse events) in QALY terms.
   - Issue: Based on mechanism or signal from trials; low probability; little data in trials—can be “minor” but important or serious (e.g., Vioxx)
   - Can use time-trade off or discrete choice analysis to measure.

   - Issue: At pre-approval, may have no clues about these
   - Approach: subjective probability and valuation based on historical data and expert judgment.
Recommendation

We should more fully evaluate the feasibility and usefulness of an **explicit, transparent process** of risk-benefit measurement relying on bioclinical health outcomes **models**:

» At pre- and post-approval (if there is a continuing issue).
» Using quality-adjusted life years (**QALYs**) as common metric (in most cases) to assess **Population Health Impact**.
» If delay to gather more safety data is recommended, the model should explicitly calculate the potential benefits lost.
» It may not be reasonable to apply the full methodology in the same depth for every product.
» Always remember that individual preferences matter and will vary.
Issues for further consideration

1. What is the appropriate sponsor-agency model for this? Adversarial? Collaborative? Independent safety board?

2. How to deal with “off-label” modeling (i.e., from primary surrogate endpoints to long-term expected outcomes?

3. How to handle potential future indications and “off-label” use in the model?

4. How best to measure the QALYs associated with potential safety problems?

5. How do you account for differences in individual preferences (regarding benefit valuation and risk)?

6. How is the cost of gathering additional information considered? (Issues of “expected value of perfect information”)

7. Cost of compliance to company to follow a new guidelines.

8. Impact on development time and cost?