

Assessing the Potential Value of Pre-Marketing Quantitative Risk-Benefit Modeling of New Pharmaceuticals

*Presentation to
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Hypothesis to Explore

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, 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

à

**Long-Term
Improvements in
Surrogate Co-
Morbidity:**

- Glucose tolerance
- Cholesterol
- Blood Pressure

à

**Improved Clinical
Outcomes:**

Cardiovascular/
Cerebrovascular
Events

à

**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 toward their agenda. Public visibility of some types of mistakes could bias decisions to minimize risk, rather than making the right balance. Why?
 - » **Type I errors** (inappropriately approving a drug that eventually has safety problems) are visible.
 - » **Type II errors** (keeping a beneficial drug off the market) are mostly invisible.
- What can be done to help find the right balance?
 - » See the three risk guidances and comments.

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 preference?

Incremental Net Health Benefit (INHB) of New Drug (2) vs. Current Therapy (1)

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

where

- » Effectiveness E is measured in QALYs
- » Risk R is measured in QALYs

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

But these measures are uncertain and would have variances around them \rightarrow 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.
2. Measuring **unknown**, serious, rare side effects in QALY terms.
 - 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).
 - » If delay to gather more safety data is recommended, the model should explicitly calculate the potential benefits lost.
 - » It may not be reasonable or necessary to apply the full methodology in the same depth for every product.
- » In other words, we need to do a cost-effectiveness analysis using this proposed approach—a CEA of this quantitative RBA approach.

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?

Appendix Slides

FDA's Risk Guidances (March 2005)

- Three guidances: Premarketing, RiskMAP, Pharmacovigilance
- Preamble: “Specifically, risk management is an iterative process of (1) assessing a product’s **benefit**-risk balance, (2) developing and implementing tools to minimize its risks while preserving its **benefits**, and (3) evaluating tool effectiveness and reassessing the **benefit**-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve risk-**benefit** balance. This four-part process should be continuous throughout a product’s lifecycle, with the results of risk assessment informing the sponsor’s decisions regarding risk minimization.” (Emphasis added)

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)

On Benefits and Risks—from FDA RiskMAP Guidance (March 2005)

- “Benefits and risks are difficult to quantify and compare because they may apply to different individuals and are usually measured and valued differently.”

International Society of Pharmacoeconomics and Outcomes Research (ISPOR)

Comments on the Draft Concept Papers

- “Better outcome measures may aid in improving FDA’s ability to understand the the Benefit-Risk ratio. . . .”
- “The use of pharmacoeconomic modelling may be applied to risk benefit decision making. . . .”
- “Outcomes assessment may also help companies in the development of, and evaluation of, risk management plans.”
- Development and evaluation of tools will require a strong research base.

“Benefit-Risk in Perspective”

Lynn Bosco of AHRQ at ISPOR, May, 2004

- “The critical bottom line: we cannot consider risk management outside the context of understanding benefit.”
- “We cannot understand benefit without understanding associated risk and finding a way to compare it in similar metrics..the elusive benefit to risk ratio.”

Are QALYs the only way to measure risks and net health benefits and trade-offs in commensurate units?

- **NO**—other methods may be better for specific problems:
 - » Monetary valuation using contingent valuation or discrete choice techniques. (E.g., for short-term, low-cost acute illnesses.)
 - » QALYs are most widely used type of HALY—health-adjusted life year, others include disability-adjusted life years (DALYs) and Healthy-Year Equivalents (HYEs)
 - » Risk trade-offs

Other References

- Walker S and Cone M. “Benefit-Risk Assessment: Summary Report on the Workshop on The Development of a Model for Benefit-Risk Assessment of Medicines Based on Multi-Criteria Decision Analysis” CMR International, March 2004.
- Lynd L et al. “A Systematic Review and Critical Evaluation of Harm-Benefit Analysis Method for Therapeutic Interventions” Presented at SMDM Meeting, 2005.
- Lynd LD and O’Brien BJ “Advances in risk-benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis.” JCE, 2004.