Benefit-Risk Assessment and Comparative Effectiveness Research
- Are they really converging?
…what does market access have to do with it…

Basel Biometric Society, September 25, 2012
Benefit-Risk & Comparative Effectiveness Seminar
Fred Sorenson
Acknowledgments & Disclaimer

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Disclaimer:

The views and opinions contained in this presentation reflect those of the speaker, and should in no way be considered expressly those of the BBS nor of the contributors cited above.
A Bit of Background

In 5 years, all statisticians will be involved in drug safety
Stephen Evans, Eur. DIA biostatistics meeting, Venice, Italy 2002

In 5 years, all statisticians will be involved in health economics
David Sugano, Eur. DIA biostatistics meeting, Heidelberg, Germany 2006

2 burning issues facing the heads of biostatistics in pharma are drug safety and HTA
EFSPI Stats Leaders meeting, Berlin 2010
Agenda

1. Market and Political Environment:
   … the pharmaceutical and medical device industry’s need for a well-defined role for benefit-risk assessment and CER is driven by external environmental changes and internal challenges

   … pharmaceutical companies have integrated benefit-risk into clinical development, but primary aim for registration remains the status quo and has led to suboptimal market access that CER should help to alleviate

3. Case Study – Rosiglitazone

4. Implications and Applications:
   … failure to demonstrate “real-world” evidence obtained through benefit-risk assessment and CER will result in cost-cutting measures and other restrictions to market access for new products and technologies
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2. Benefit-risk and CER in Product Development and Commercialization – Some common ground?
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Market and Political Challenges

The existing “Operating Business Model” in pharma is challenged by globally declining market growth rates, along with increasing costs and diminishing returns.

Market growth is driven primarily by specialist products, however high prices for speciality products have resulted in efforts by governments to limit volumes of prescription and price.

Benefit-risk assessment is considered a component part of value-driven drug development, and essential in achieving regulatory approval, whereas comparative effectiveness research is most commonly directed at reimbursement and payers as products are subjected to health technology assessments (HTAs) post-approval.

However, the important role both play in R&D and commercialization is often still not being fully recognized within companies.
Clinical trials are commonly designed with scientific objectives and endpoints to meet regulatory Market Authorization approval requirements. However, many drugs satisfying efficacy, safety, quality criteria and approved by Regulators, eventually fail to provide value to Heath Technology Assessment (HTA) Bodies and ultimately Payers. Pricing, Coverage & Reimbursement which must now be seen as integral parts of a “full” drug development process.

HTA Bodies and Payers are today demanding more data to translate efficacy/safety data promise from clinical trials into expected effectiveness vs. current standard of care in clinical practice.

This increasingly complex environment demands that pharmaceutical companies make critical decisions on how clinical trials should be better designed and equipped with the right tools to ensure that they will generate relevant and measurable data for key healthcare stakeholders.

Companies are then able to provide evidence-based value propositions and generate data needed for pricing agreements. In addition, they have then the evidence to demonstrate their products’ superior health outcomes and benefit-risk profile against comparators, and thus optimize commercialization.

Key Message
An Organization needs to anticipate and react early to potential future requirements to alleviate tensions between clinical outcomes and HTA Bodies’/Payers’ expectations.
US landscape is changing with American Recovery and Reinvestment Act of 2009
Challenges & Strategic Imperatives for the Industry

**Patent Exposure**
- Operational Flexibility & Resource Bandwidth
- US / Japan / ROW Commercial Presence
- Recent Development Failures
- Pipeline Maturity Sub-optimal
- Maximisation of Pipeline Launch Potential $$
- Increasing Market Access demands from HTA bodies & Payers
- Rapid New Product Uptake
- Operational Flexibility & Resource Bandwidth
- US / Japan / ROW Commercial Presence

**Critical Success Factors**
- Maintain top line growth
  - Partner/Acquire (Companies, Compounds, Brands)
  - Target high growth CNS sectors / Diversify
  - Influence clinical guidelines
- Cut costs to improve short term earnings
  - Administration
  - Sales & Marketing resource
  - Build flexible resource model

**Optimize Portfolio Strategy**
- Primary vs. secondary care
- Maximise commercial potential of pipeline assets
- Incorporate Market Access stakeholders perspectives alongside traditional KOLs in guiding R&D decisions and priority setting
- Globalise business
  - Strengthen US / Japan position
  - Global Brands / molecules

**Company Imperatives**
Agenda

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   … the industry’s need for a well-defined role for health economics is driven by external environmental changes and internal challenges

2. Benefit-risk and CER in Product Development and Commercialization
   – Some common ground? - :
   … pharmaceutical companies have integrated benefit-risk into clinical development, but primary aim for registration remains the status quo and has led to suboptimal market access that CER should help to alleviate

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Benefit-Risk and CER serve the value and safety channels
R&D Alignment With Payer Perspectives Is Sub-Optimal Across The Industry

Integrating Health Economic input early in clinical development is important to optimize value in the marketplace.

**Traditional State**

- **Clinical**
  - Science driven - Efficacy and Safety
  - KOL input and internal medical perspective only
  - Silo approach - Limited communication prior to hand off from clinical to launch team
  - Bonus scheme for researchers based on regulatory approval

- **Commercial**

**Convergent State**

- **Clinical & Commercial Convergence**
- Cross-functional Interactions

- **Value Drivers**
  - HTA driven - Effectiveness and Efficiency
  - Expanded clinical input from a wider range of external stakeholders
  - Transversal interactions - earlier understanding of key customer needs
  - Bonus scheme for researchers incorporate market access/reimbursement criteria

**Silo Approach**

- Pre-Launch
- Launch
- Post-Launch

**Clinical & Commercial**

- Pre-Launch
- Launch
- Post-Launch
A Robust Product Value Proposition is Critical in Development
Planning a variety of studies
- Burden of illness (observational)
  - Understanding epidemiology

Randomized Controlled Trials (interventional)
- Design considering regulatory and payer requirements

Chart reviews (observational)
- E.g. Resource utilization

Existing database analyses (observational)
- E.g. Pharmacovigilence
Lack of therapeutic innovation cannot be compensated by promotion anymore……

- Ultimate success in the market place is driven by the relevance & strength of clinical & economic evidence provided to payers.

- Cost-effectiveness evidence requires relevant and persuasive clinical evidence, often requiring a comparison against standard care.

- Pricing & Market Access challenges are often directed at the clinical evidence base.

- Payers’ clinical & economic evidence needs should be considered in constructing the clinical development plan well before Phase III.

- DATA, DATA, DATA.
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Some causes of uncertainty and evolving data

- BR assessment and corresponding decision must synthesize numerous endpoints and reconcile variable data quality…can compromise the transparency, objectivity & rigor.

- Implied linkages between short-term effects (e.g., CD4, HbA1c) and their purported sequelae.

- Benefit and risk effects are analyzed separately and statistically (clinical relevance implied).

- Main way to address uncertainty: more data!
Health Outcomes Model: connecting the dots

Example from Type 2 diabetes

<table>
<thead>
<tr>
<th>All RCTs</th>
<th>Most RCTs</th>
<th>Some RCTs</th>
<th>Few RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug effect</td>
<td>Intermed outcomes</td>
<td>Clinical outcomes</td>
<td>Final outcomes</td>
</tr>
<tr>
<td>Blood glucose control</td>
<td>Retinopathy, Nephropathy, Neuropathy</td>
<td>Blindness, End stage renal disease, Amputation</td>
<td>Survival, Death</td>
</tr>
</tbody>
</table>

Pre-approval | Post-approval | UKPDS, Epi studies
Framing the CBR Assessment: clinical/regulatory context

- **Glyburide** (approved 1984):
  - Benefit: Glucose control, but tends to be less “durable”
  - Risk: Hypoglycemia, weight gain

- **Metformin** (approved 1995):
  - Benefit: Glucose control; without hypoglycemia and weight gain
  - Risk: Lactic acidosis?
  - First-line pharmacotherapy

- **Rosiglitazone** (approved 1999):
  - Benefit: Superior to placebo, non-inferior to glyburide
  - Risk: Hepatotoxicity? (troglitazone pulled from market); edema
  - 2nd in class
What changed between 1999 and 2007?

In 2007:

• 5-year data: more durable glycemic control vs other drugs
• hepatotoxicity seen in troglitazone no longer a concern for Avandia
• CHF confirmed…MI/CV death?
Incremental Net Health Benefit (INHB)

- Aggregate an array of outcomes using a metric that combines *quality of life (utility)* and *length of life*.
  - Quality-adjusted life-year (QALY)

- Net Health Benefit = $\sum_{\text{Benefits}} - \sum_{\text{Risks}}$

- Incremental NHB = $\text{NHB}_{(\text{drug A})} - \text{NHB}_{(\text{drug B})}$

Utility over a Patient’s Life Cycle

Perfect health

Quality of life

Death

Age

0 10 20 30 40 50

BBS Seminar Benefit-Risk & CER / September 25, 2012 / FS
Methods: Model Overview

- CORE-IMS diabetes model

# Methods: Sources for Key Model Inputs

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>1999</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td><strong>Glycemia (HbA1c)</strong></td>
<td>Phase 3 trials</td>
<td>ADOPT study</td>
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<tr>
<td><strong>Utilities</strong></td>
<td>UKPDS (EQ-5D)</td>
<td>UKPDS (EQ-5D)</td>
</tr>
<tr>
<td><strong>P(severe hypoglycemia)</strong></td>
<td>Phase 3 trials</td>
<td>ADOPT study</td>
</tr>
<tr>
<td><strong>P(die)</strong></td>
<td>Hospital-based retrospective study</td>
<td>Hospital-based retrospective study</td>
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<tr>
<td><strong>P(fulmin. liver failure)</strong></td>
<td>Troglitazone reports</td>
<td>N/A</td>
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<tr>
<td><strong>P(die)</strong></td>
<td>FDA testimony</td>
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<tr>
<td><strong>P(pulmonary edema)</strong></td>
<td>Phase 3 trials</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>P(CV death)</strong></td>
<td>N/A</td>
<td>FDA meta-analysis</td>
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</table>
## Results, 1999

<table>
<thead>
<tr>
<th></th>
<th>Life-Years</th>
<th></th>
<th>QALYs, discounted</th>
<th></th>
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<td></td>
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<td>GLY</td>
<td>PBO</td>
<td>RSG</td>
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<tr>
<td>Harms</td>
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<td>0.001</td>
<td>0.000</td>
<td>0.003</td>
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<tr>
<td>INB</td>
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<td>-0.312</td>
<td>0.639</td>
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</table>

INB: Incremental net benefit.
INB >0 favored RSG. INB <0 favored comparator.
Results, 2007

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<tbody>
<tr>
<td></td>
<td>RSG</td>
<td>GLY</td>
</tr>
<tr>
<td>Harms</td>
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<td>0.001</td>
</tr>
<tr>
<td>INB</td>
<td>--</td>
<td>0.222</td>
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</tbody>
</table>

INB: Incremental net benefit.
INB >0 favored RSG. INB <0 favored comparator.
Sensitivity Analyses from 1999 Data

Incremental NB (disc.QALYs):
RSG - PBO, 1999

- Hba1c +/- 95% CI
- p(noAE>sev hypo)
- p(ACPE>die)
- p(noAE>ALF)
- p(noAE>ACPE)
- 1yr v 10 yr risks
- p(hypo>die)
- p(ALF>die)

Incremental NB (disc.QALYs):
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RSG-GLY, 2007

- p(CV death)
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- Hba1c +/- 95%CI
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- p(hypo>die)

Incremental NB (disc. QALYs):
RSG-MET, 2007

- p(CV death)
- 1yr v 10 yr risks
- Hba1c +/- 95%CI
- p(noAE>sev hypo)
- p(hypo>die)
Conclusions: transparency of assumptions

- Rate of rise in HbA1c was linear. (UKPDS, FDA)

- CV events while on glyburide or metformin were disease-related, not drug-related. (labeling)

- Did not evaluate combination therapy.

- Probability of harm was not time-varying.

- Risk of adverse events only for 5 years. (UKPDS)

- Only fatal adverse events modeled (excluded harms such as bone fracture and lactic acidosis).
Conclusions: evolving data and uncertainty

• One can explore the effect of uncertainty in individual parameters and in aggregate on overall CBR. Goes beyond trial context.

• The FDA might have reconsidered initial (1999) approval for monotherapy given efficacy data? Would have sought longer trials?

• Given uncertainty from CV risks, findings upheld past ADA guidelines recommending metformin as the first-line monotherapy.
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Evidence will always remain the primary foundation
### Patient Fears
- Restriction of patient access to expensive treatments
- Allowance of government to use CER to make cost-benefit calculations and focus on cost containment data rather than clinical evidence

### Recent Examples
- **New Zealand**
  - New Zealand’s CER Agency, Pharmac took 5 years to approve the use of the anti-cancer drug Herceptin
- **Britain**
  - NICE denied approval for several cancer drugs widely available in other countries because of cost
- **U.S.**
  - FDA approved Avastin in 2008 but it revoked the indication for advanced breast cancer, claiming it does not extend life long enough overall
  - Provenge initially approved for Medicare coverage for “on label” use only

### The Unknown
- Cost-effectiveness decisions are prohibited under PPACA from being used as sole basis for denying coverage in federal programs, and
- Cost-effectiveness thresholds for coverage are barred
- PCORI may not use a “dollars-per-quality adjusted life year . . . as a threshold”
- A patient centered approach to generating evidence would support personalized medicine
- More effective treatments may increase the overall costs, not necessarily reduce costs
Build A Consistent Product Value Proposition
Combining Various Aspects Into A Single And Consistent Entity

- Hard Evidence of Real Unmet Patient Needs
  - Clinical differentiation
    - Comparative Effectiveness
    - Safety / Tolerability
    - Patient Quality Of Life
    - Convenience & Compliance
  - Economic differentiation
    - Healthcare Budget impact
    - Cost effectiveness
    - Quality-of-life value
    - Targeted sub-populations

Evidence-based Pricing Strategy

MA VALUE PROPOSITION

Regulatory Agencies

HTA bodies

Patients

Prescribers

Payers
Several initiatives are already in place

**INITIATIVES TO DEMONSTRATE REAL-WORLD VALUE:**

**STROBE (Risk-Benefit)**
- 22-point checklist of factors to include in an accurate and complete report of an observational study

**OMOP (Risk-Benefit)**
- Public-private methods development and testing consortium taking a 2-tiered approach

**ISPE (Observational/Pharmacoepidemiologic)**
- Address protocol development, responsibilities, study conduct, communication, adverse event reporting, and archiving
- An earlier FDA document had similar objectives

**Sentinel Initiative (Safety)**
- Focused on real world long-term safety and risk data based on retrospective analysis of claims data

**CMS (Evidence of Value)**
- Manifested by its national coverage decisions that recommend ‘coverage with evidence development’
Conclusion

Benefit-Risk and Comparative Effectiveness Programs for Regulators and Payers should both:

• Foster a strong collaboration between Clinical R&D, Drug Safety, Health Economics and Marketing with strong biostatistics (quantitative) support in all areas

• Define clear roles and responsibilities to make the most effective use of expertise, skills and resources

• Contribute more case studies on how methodologies are best applied and influence decision making
Benefit-Risk and Comparative Effectiveness Programs for Regulators and Payers should both:

- Enable effective communication of value evidence generation activities across the whole product life-cycle

- Provide for early engagement and cross-functional alignment on regulatory and market access hurdles

- Be flexible and adaptable to meet a complex and evolving global market environment and still meet needs of patients with best available cost-effective care
References


Thank you for your attention