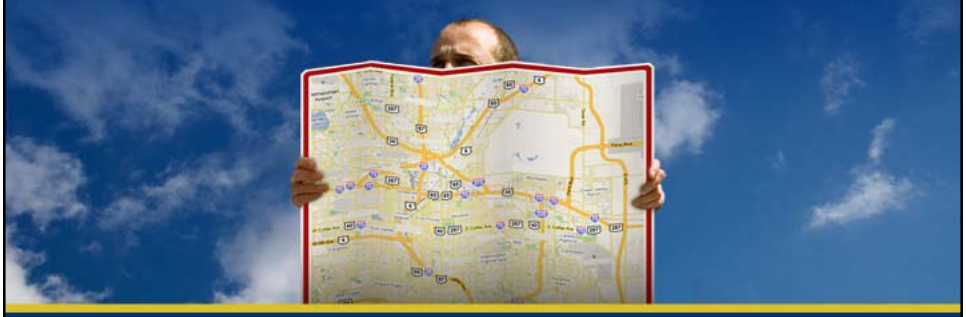
From Resilience To Growth:

Mapping a New Direction for Life Sciences & Medical Devices



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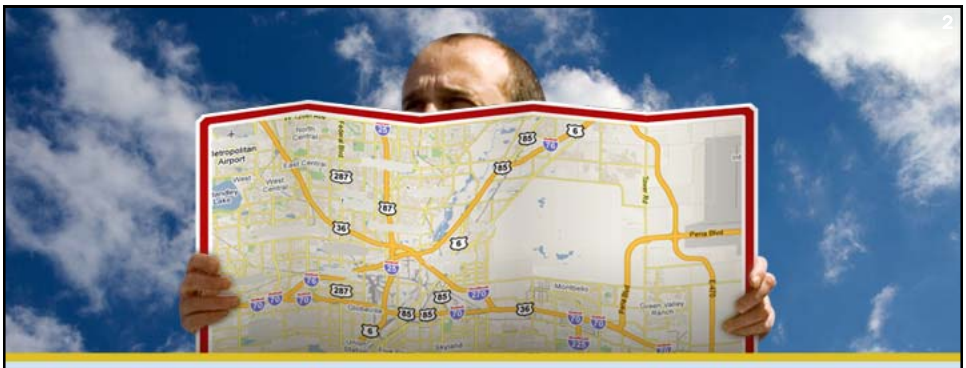

Growth Strategy: Evidence Based Reimbursement & Commercialization Strategies for Innovators & Investors

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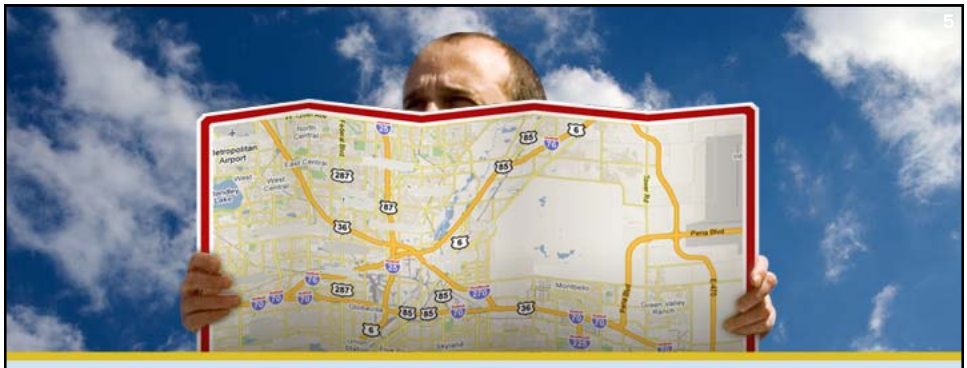
Panelists:

- **Judith A. Waltz**, Partner, Co-Chair, Life Sciences Industry Team and member, Government Enforcement, Compliance & White Collar Defense Practice, *Foley & Lardner*
- **Antoun Nabhan**, J.D., Senior Director, Corporate Development, *Onyx Pharmaceuticals*
- **Anita Chawla**, Ph.D., Vice President, *Analysis Group*

Road Map

- Legal overview of recent developments in product coverage (Judy)
- Proper planning for product coverage (Antoun)
- Impact on financing / licensing (Antoun)
- Data that should be in place for coverage (Anita)
- Preparing comparative effectiveness data (Anita)



Comparative Effectiveness

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2010 Affordable Care Act (ACA)

- Patient Protection and Affordability Act and Health Care and Education Reconciliation Act (Pub.L. 111-148, a/k/a H.R. 3590, and Pub. L. 111-152, a/k/a H.R. 4872) – finalized by President Obama's signatures on March 23 and 30, 2010
- Consolidated language compiled by the House Legislative Counsel now available at http://www.premierinc.com/about/advocacy/issues/10/healthcarereform/PPACA-CONSOLIDATED.pdf
- Foley.com/HCReform (resource site)

"Comparative Effectiveness Research is out; Patient Centered Outcomes Research is in."

- As congressional debate on creating a public/private entity to conduct such research was heating up, Senate Finance Committee Chairman Max Baucus (D-Mt.) Baucus decided that the term "comparative effectiveness research" was becoming too much of a lightning rod for controversy and changed the term in health care reform legislation to "patient-centered outcomes research."

Gregory Twachtman, The RPM Report, *"What's In a Name? The Semantics of CER"* (September 10, 2010)

Comparative Effectiveness Research

- Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care.

Comparative Effectiveness Research (cont.)

- There are two ways that this evidence is found:
  - Researchers look at all of the available evidence about the benefits and harms of each choice for different groups of people from **existing** clinical trials, clinical studies, and other research. These are called research reviews, because they are systematic reviews of existing evidence.
  - Researchers conduct studies that generate **new** evidence of effectiveness or comparative effectiveness of a test, treatment, procedure, or health-care service.

Source: http://effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/

Comparative Effectiveness Research (cont.)

- Seven steps are involved in conducting this research and in ensuring continued development of the research infrastructure to sustain and advance these efforts:
  - Identify new and emerging clinical interventions
  - Review and synthesize current medical research.
  - Identify gaps between existing medical research and the needs of clinical practice
  - Promote and generate new scientific evidence and analytic tools

Comparative Effectiveness Research (cont.)

- Train and develop clinical researchers.
- Translate and disseminate research findings to diverse stakeholders.
- Reach out to stakeholders via a citizens forum.

Source: AHRQ website

Patient-Centered Outcomes Research Institute (PCORI)

- ACA Section 6301.
- Nonprofit corporation.
- Will identify national priorities for research.
- Will assist in the analysis of health outcomes and the clinical effectiveness, risks, and benefits of more medical treatments such as therapies, diagnostic tools, and pharmaceuticals (e.g., drugs and biologics).

Patient-Centered Outcomes Research Institute (PCORI) (cont.)

- The research funded must take into account, as appropriate, the potential for differences in the effectiveness of health care treatments in various subpopulations; for example, individuals with different genetic and molecular sub-types.
- Results of the studies are to be published in a format that is comprehensible to patients and providers, with safeguards to protect patient privacy and confidentiality of study subjects.

AARA Funds PCORI

- AARA (aka Stimulus Bill) signed by President Barack Obama in February 2009, authorized $1.1 billion for research on what medical treatments work best for which people. (AARA split funding between the Agency for Healthcare Research and Quality (AHRQ); National Institute for Health (NIH), and HHS.
- $17 million of ARRA funds will be used to establish a network of PCOR centers. PCOR stands for "patient-centered outcomes research," also known as "comparative effectiveness research."

AARA Funds PCORI (cont.)

- "Patient-centered outcomes research can improve health outcomes by developing and disseminating evidence-based information to patients, providers and decision-makers about the effectiveness of different treatments," said HHS Secretary Kathleen Sebelius.

HHS Press Release, *"HHS Awards $17 Million for Patient-Centered Outcomes Research"* (Sept. 1, 2010).

PCORI Parameters

- PCORI may not mandate coverage, reimbursement, or policy recommendations.
- HHS is prohibited from denying coverage based solely on PCORI research.
- HHS may not use PCORI research in a way that treats extending the life of elderly, disabled, or terminally ill patients as of lower value than for a person who is younger, non-disabled or not terminally ill.

PCORI Parameters (cont.)

- The institute is prevented from developing or using "a dollars-per-quality adjusted life year (or similar measure that discounts the value of a life because of an individual's disability) as a threshold to establish what type of health care is cost effective or recommended."

Medicare – Historical Approach

- Coverage with Evidence-Based Development
- Least Costly Alternative
- Trend towards focus on "outcomes" as part of the quality initiative
- FDA/CMS Sentinel Initiative – shared information about the Medicare population
  - 2011 Budget Justification – focus on increased sophistication of data collection/use so as to be a leader in comparative effectiveness

WellPoint Standardizes Comparative Research Guidelines

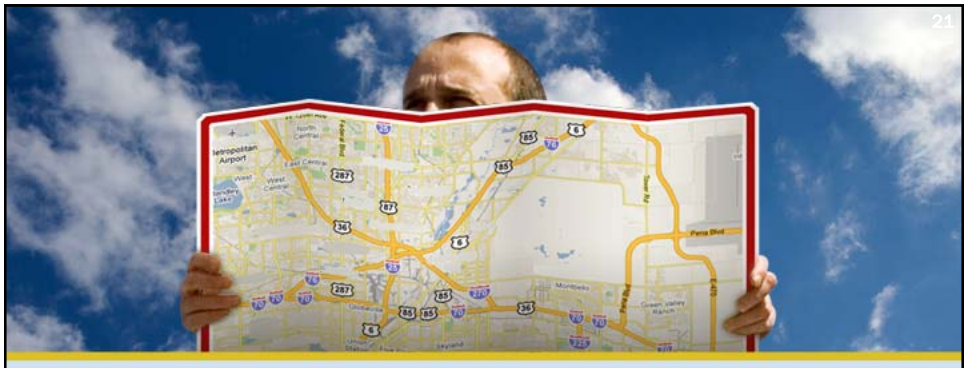
- Indianapolis-based WellPoint Inc. (NYSE: WLP) says it has become the first health benefits company to standardize comparative effectiveness research (CER) guidelines for drug evaluation. The company says CER can be used to help determine the co-pay charged to members of its affiliated health plans.

Source: InsideINdianaBusiness.com Report (updated: 5/20/2010)

Roadblocks to CER/PCO Approach

- Who pays for the clinical trial to gather comparative data?
- Co-pay differentials encourage patient choices among drugs tested.
- How do you bill for an unknown drug, and get to unidentified claims on patient EOBs?
- Statutory authority for alternative payment mechanisms under Medicare, but not implemented.

Martin, McGuire and Fine,"*Roadblocks to Comparative-Effectiveness Research,*" N. Engl. J. Med. 363;2 (July 8, 2010)



Implications for R&D-Stage Companies

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A Better Mousetrap? Better Bring Data!

- Now more difficult for R&D-stage companies to shift reimbursement risk
  - Acquisition comes at later stages
  - IPO market still frozen
- Ex-U.S. regulatory processes incorporating comparative effectiveness thinking
  - Ex-US markets are an increasing share of your product value
- Your funders and buyers are making decisions based on this:
  - "Can we sell it"?
  - "Can we sell it to companies who will sell it"?

Implications for Partnering

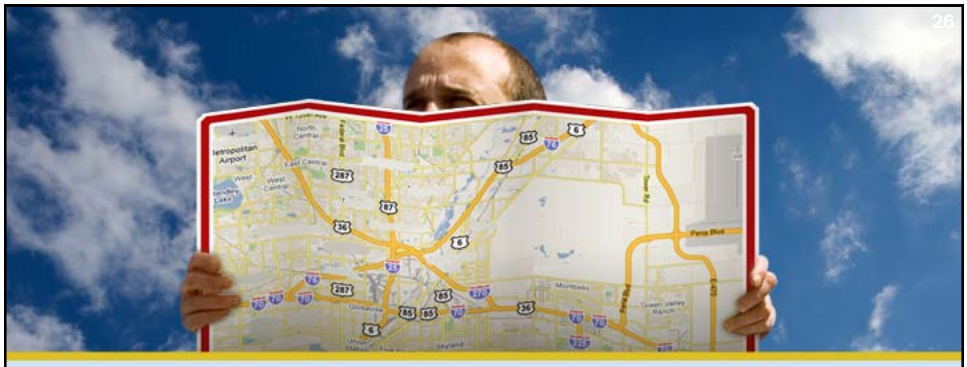
- "Me too" drugs will be increasingly difficult to partner without randomized controlled study data
- Companion diagnostics & biomarker-driven trial strategies will be easier to partner
- Mgm't teams should anticipate deep diligence around reimbursability and comparative effectiveness → be prepared with research & data
- A higher bar for deals (maybe)…
  … but deals that meet the bar will get improved economics than in the past

Implications for Financing

- Investors know they will own companies for longer
- Partner / acquirer concerns central to investors also
  - Demand for innovation
  - Demand for biomarkers to compare to SOC
  - Demand that managers anticipate CE in clinical trial plans, etc.

Implications for Financing (cont.)

- Expect a need to demonstrate more groundwork for reimbursement at Series B/C stages
  - Budget for pricing & reimbursement consulting
  - Speak to global launches & by-region value



Growth Strategy: Evidence Based Reimbursement and Commercialization

Strategies for Innovators and Investors

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Demands Associated With Evidence Based Reimbursement and Commercialization Have Created a New Environment

2000	2010
Clinical Utility – Primary focus on clinical safety & efficacy (inc. surrogate endpoints) – Most likely placebo comparator	**Clinical Utility** – Primary focus on clinical safety & efficacy around patient outcomes – Increasing instance of active comparator
Eligible Patients – Blockbuster orientation toward broad patient populations	**Eligible Patients** – Patient selection a critical variable for outcomes and value proposition
Market Access – Generally assumed if safety and efficacy meet regulatory hurdle	**Market Access** – *Access not a "given" in most areas, regardless of regulatory outcome*
Commercial Potential – Focus on market share as a function of clinical comparison to SOC	**Commercial Potential** – *Economic value vs. competition plays a more important role in access and share gained*

Drivers for Evidence Will Impact Both Large and Small Firms

- Global economic conditions increase pressure for cost containment
- Increasingly competitive global markets with more payer scrutiny will demand stronger evidence packages
- Compelling evidence of value for must be generated for multiple stakeholders —physicians, patients, and payers

Drivers for Evidence Will Impact Both Large and Small Firms (cont.)

- **Large pharmaceutical and biotechnology firms**
  - Commercialize products
  - Licensees or acquirers of products developed by smaller firms
- **Smaller pharmaceutical and biotechnology firms**
  - Compete for scarce funding
  - License or sell assets
- **Investors**
  - Must be prepared to evaluate strength of an asset's value proposition, particularly in the context of reimbursement

For Manufacturers, Earlier Planning Increases Degrees of Freedom and ROI

Phase 1 → Phase 2 (early) → Phase 2 (late) → Phase 3 → Launch

- **Typical Early-Phase Issues**
  - Trial design, optimal set of metrics to support market access and physician choice
  - Patient sub-groups most likely to benefit
  - Indication sequencing
  - Prioritization of development resources, go/no go decision making
- **Value Planning and Payer Research**
  - Early pricing and market landscape assessment
  - Assess evidence based review of analogues
  - Test positioning with stakeholders
  - Health outcomes simulation modeling
- **Typical Late-Phase Issues**
  - Optimal gross/net pricing
  - Refined stakeholder value propositions, positioning, and messaging
  - Post-marketing study planning
  - Identification of resources required for launch (manufacturing, sales, etc.)
- **Value Planning and Payer Research**
  - Quantitative pricing analysis
  - Market access and contracting strategy

Early planning for coverage and reimbursement also demonstrates this issue has been addressed in the clinical development plan

General Approach to Planning for Evidence Based Reimbursement and Commercialization

Landscape and Stakeholder Assessment →	Gap Assessment and Value Strategy →	Planning
▪ *Assess market landscape and stake-holder perspectives* ▪ *Characterize context and performance requirements for successful product*	▪ *Evaluate gaps between TPP, anticipated or available evidence, and stakeholder expectations* ▪ *Set value objectives and strategy*	▪ *Develop functional tactical plans, with defined accountability* ▪ *Specify planned activities and deliverables to fulfill value strategy*

To Inform Planning, Manufacturers Can use WellPoint's Guidelines on How it Will Use CER to Make Formulary Decisions

WellPoint Evaluation Criteria

1. Undertake Critical Appraisal of the Evidence (Critical Review of the Clinical Trial Data)
2. Determine the Clinical Value of a Drug
   - High-quality evidence is used to determine if a drug is *favorable, comparable, or unfavorable compared to another drug*
3. Solicit Clinical Specialist Review and Input

To Inform Planning, Manufacturers Can use WellPoint's Guidelines on How it Will Use CER to Make Formulary Decisions

WellPoint Evaluation Criteria (cont.)

4. Include Comparative Effectiveness Research (CER) and Observational Data
   - Analyses using integrated pharmacy, medical, and laboratory data
   - Evaluate how the drugs perform in a "real-world" setting
   - ***Focus decisions on outcomes that matter to patients, such as improved survival, reduced cardiovascular events, and reduced fractures***
   - Ultimate goal of improving quality of care, reducing total cost of care, optimizing care, and improving productivity

To Inform Planning, Manufacturers Can use WellPoint's Guidelines on How it Will Use CER to Make Formulary Decisions

WellPoint Evaluation Criteria (cont.)

5. Develop Point-of-Sale Edits
6. Evaluate the Total Value of a Drug for Formulary Tier Placement
   - Use high-quality data on ***clinical efficacy, comparative effectiveness and outcomes, member impact, and overall drug value to make informed tier placement decisions***
7. Analyze the Impact of P&T Formulary Decisions on Total Cost-of-Care and Quality Analysis

The National Comprehensive Cancer Network Published its Proposed Approach for Integrating CER Into Clinical Decision Making, Based on the NCCN Common Therapeutic Index™

NCCN's preliminary thinking about the CTI conceptual framework includes several criteria on which therapies might be scored—this information may also be used to inform planning

Efficacy

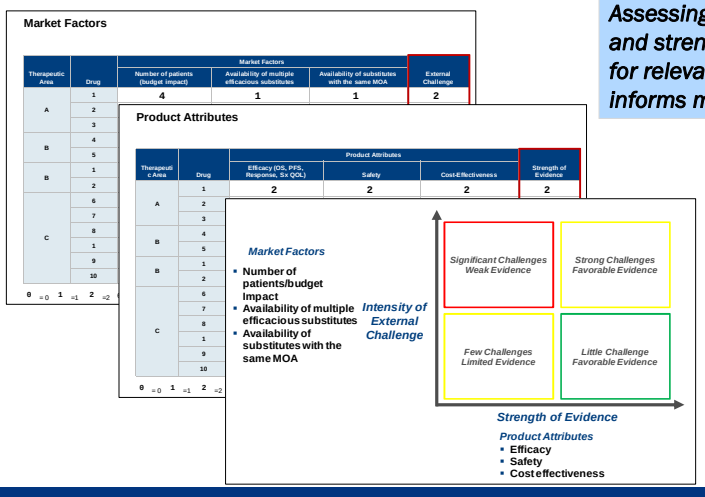
- Level of evidence
- Probability of achieving a cure
- Impact on survival (e.g., overall, disease-free, progression-free)
- Impact on disease control
- Impact on improving performance status
- Impact on disease-related symptom control

Toxicity

- Probability of fatal event
- Probability of severe, life-threatening side effects
- Duration of adverse effects (chronic vs. acute)
- Debilitation impact of adverse effects
- Impact on health-related quality of life (HR-QOL)

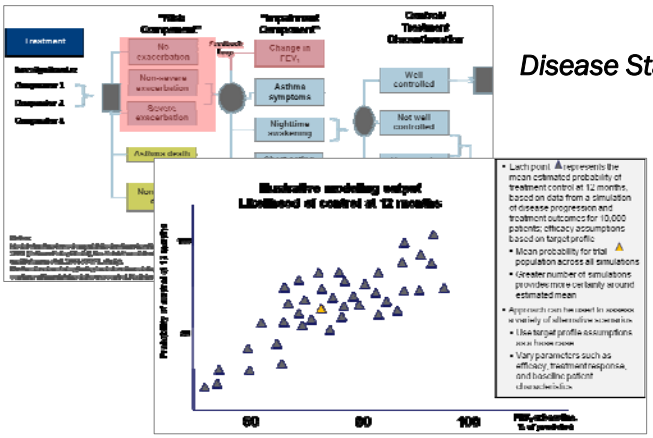
Source: Li EC, DeMartino J. Preliminary Report: The Development of the NCCN Comparative Therapeutic Index™ as a Clinical Evaluative Process for Existing Data in Oncology. *JNCCN* 2010;8[Suppl 5]:S1–S9.

CER Evaluation Criteria Can be Used to Characterize Context and Performance Requirements for a Successful Product



Assessing market factors and strength of evidence for relevant analogues informs market access risk

Modeling can Help Evaluate the Likelihood That a TPP is Favorable, Comparable, or Unfavorable Compared to Other Drugs



Disease State Model

Assess probability of efficacy outcomes

Evaluating Gaps Between TPP, Anticipated or Available Evidence, and Stakeholder Expectations Reveals Opportunities for Updating Clinical Programs

Dimension	Evidence
Product description	▪ Anticipated label information including indication, dosage, administration, etc.
Target population & place of product in therapy	▪ Disease definition, epidemiology, diagnosis, treatment guidelines ▪ Economic and humanistic burden of disease ▪ Treatment options (alternatives) ▪ Clinical position relative to alternatives
Clinical and economic outcomes	▪ Product data in context - **Systematic review and summary of published clinical and economic studies** - **Meta-analyses and HTA**
Value assessment	▪ Cost of diagnosis, treatment, monitoring, and adverse event management versus patient outcomes such as survival, events avoided, symptoms managed or alleviated, etc.
System Impact	▪ Health plan budget impact ▪ Expected penetration rate (market share)

Strengths	Weaknesses
▪ Product characteristics (e.g., MOA, mode of administration) ▪ Product claims based on evidence (safety, efficacy)	▪ Serious adverse events or safety signals ▪ Inability to claim key attribute relevant for TA
Opportunities	**Threats**
▪ External environment trends & market forces ▪ Stakeholder need that may be addressed by product ▪ Opportunities to improve positioning	▪ CER systematic review ▪ New competitive entrant –targeted, specific MOA ▪ Risk/harm/impact of potential weakened position

Payer Research Can Help Ensure the Right Evidence is Developed to Support Coverage and Reimbursement Evaluation

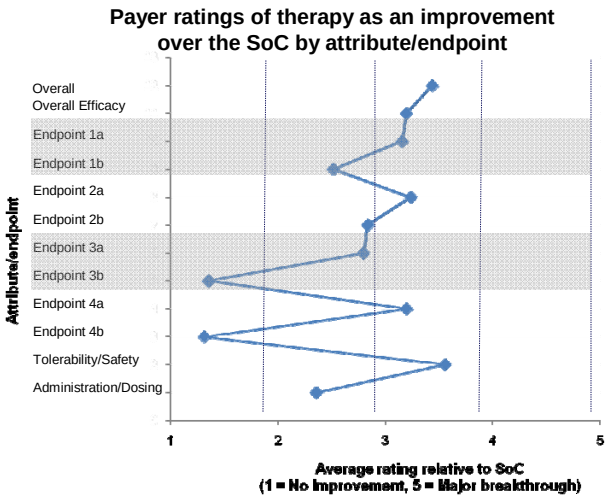
Case Study

- Business challenge
- How should a pivotal trial design be enhanced to respond to payers' needs for information about product value?

- **Key Issues**
  - No understanding of how the market would perceive the new drug from clinical or economic perspectives
- **Several areas of uncertainty**
  - Potential range of clinical outcomes
  - Degree of competition
  - Likely access and reimbursement conditions at launch in the US and leading EU countries

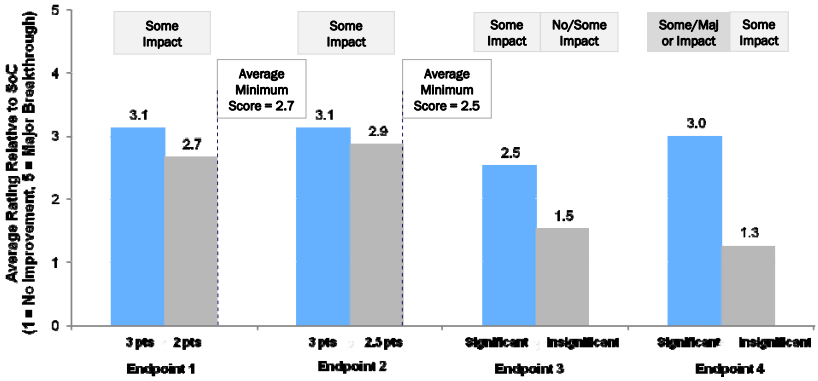
Objective: Develop an evidence-based plan for reimbursement and commercialization that integrated clinical, commercial, and economic perspectives

Payers Viewed the Profile for the New Therapy as a Substantial Improvement Over Current Standard of Care



Payers Provided Insight into Likely Market Access Given Alternative Product Profile Scenarios

Achieving no significant effect for endpoints 3 and 4 might significantly undermine access and increase restrictions for the therapy



Summary

- The environment today and in the future presents new challenges
  - Evidence for regulatory approval is no longer sufficient for optimizing market access and product uptake
- These challenges create an imperative for a different approach to developing pharmaceutical and biotechnology products
  - Strong evidence of product value, from multiple perspectives, is critical for successful market access and commercialization

Summary (cont.)

- Pharmaceutical and biotechnology companies, as well as investors, must assess critically the strength of evidence and opportunities to enhance the evidence base as product are developed — product value will depend on it

Questions??

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