The Influence of HTA in Shaping Drug Development: Investment Implications

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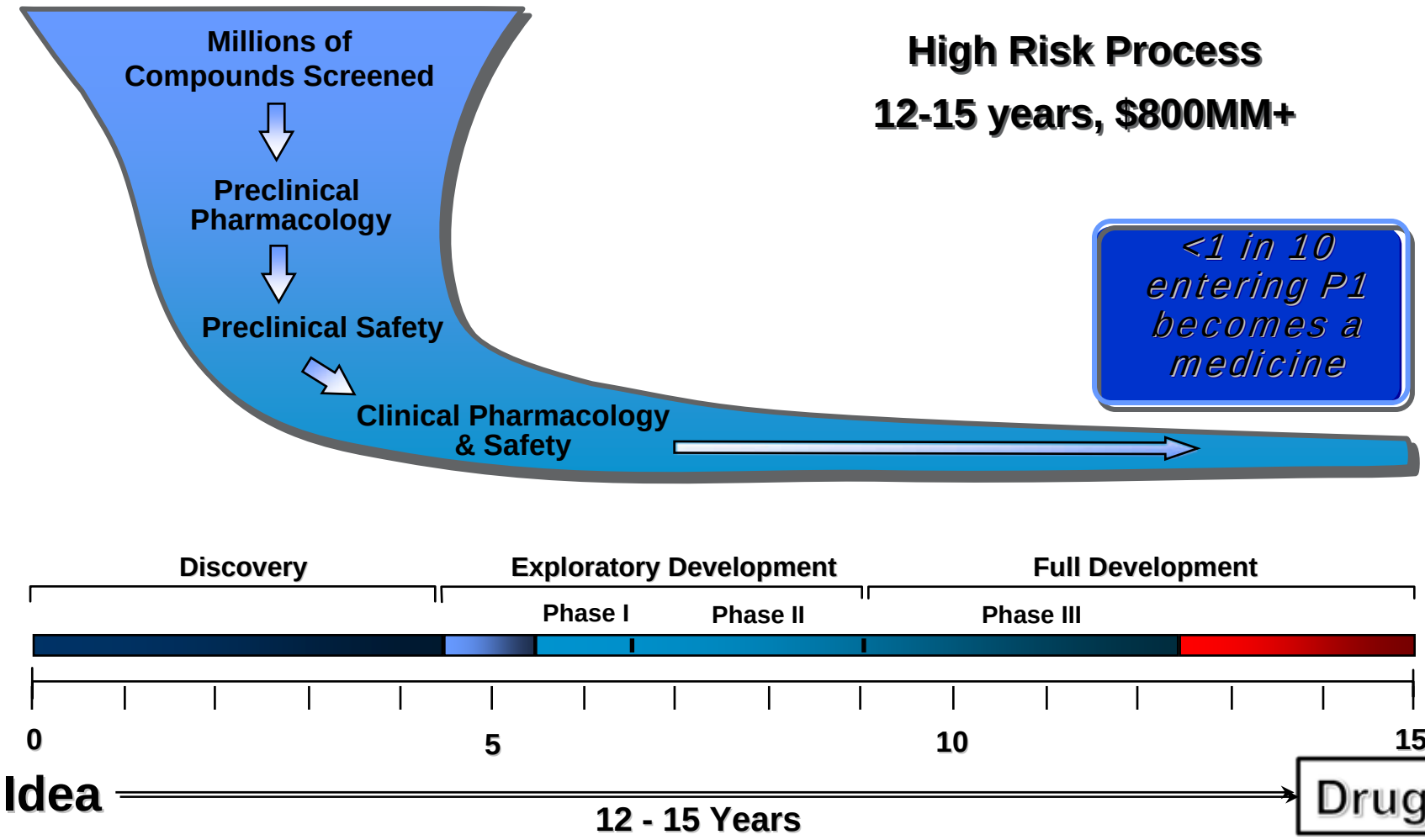
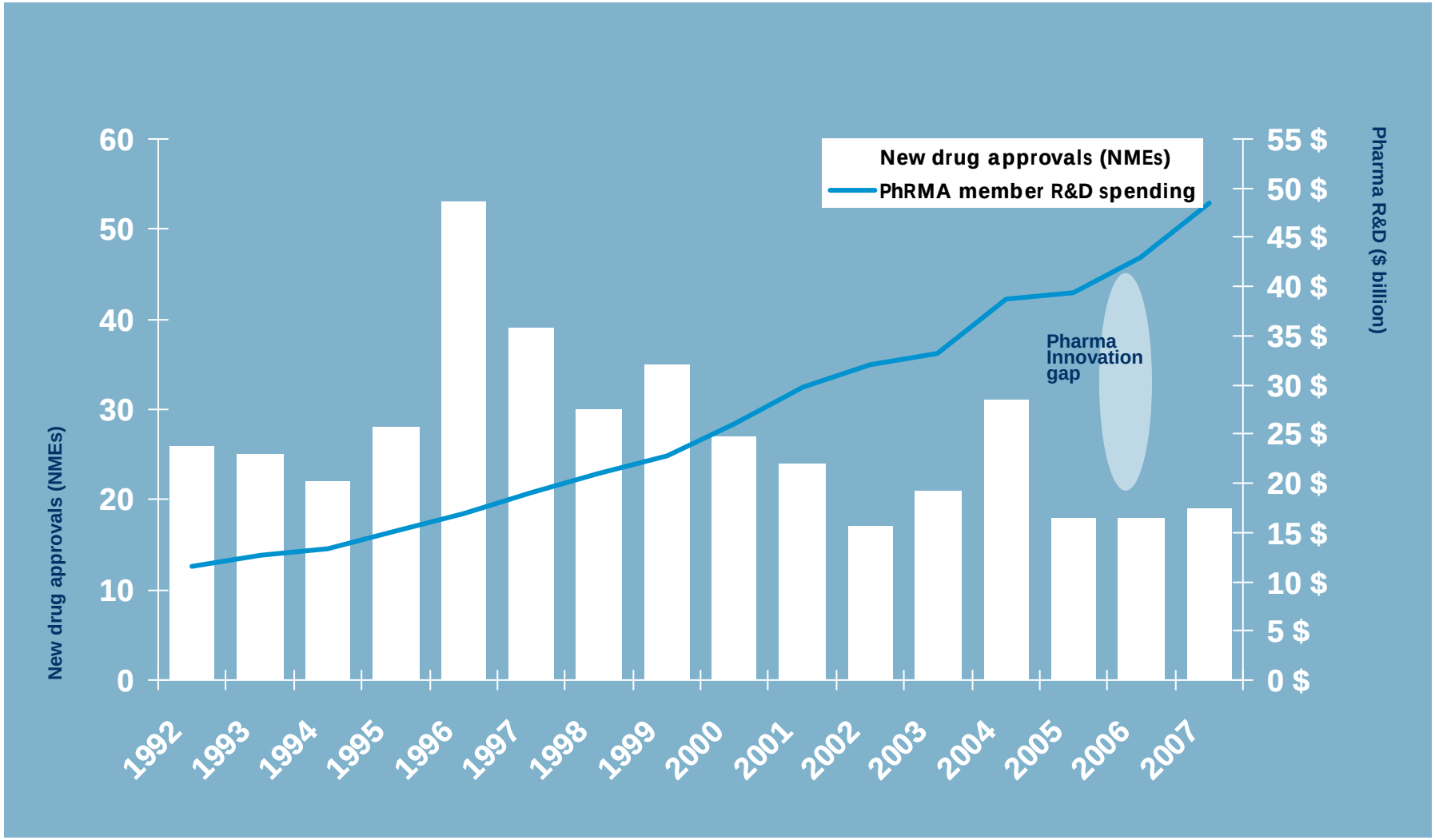
Key Points

- Drug development is risky and costly
- Regulatory approval is necessary, but no longer sufficient
- Increasing demand to provide *compelling* evidence of differentiation and *value*
- Trend towards “limited” or more rigorously managed health care budgets
- **Drug development paradigm is shifting in response to these trends**

Developing New Medicines is a Risky, and Costly, Business

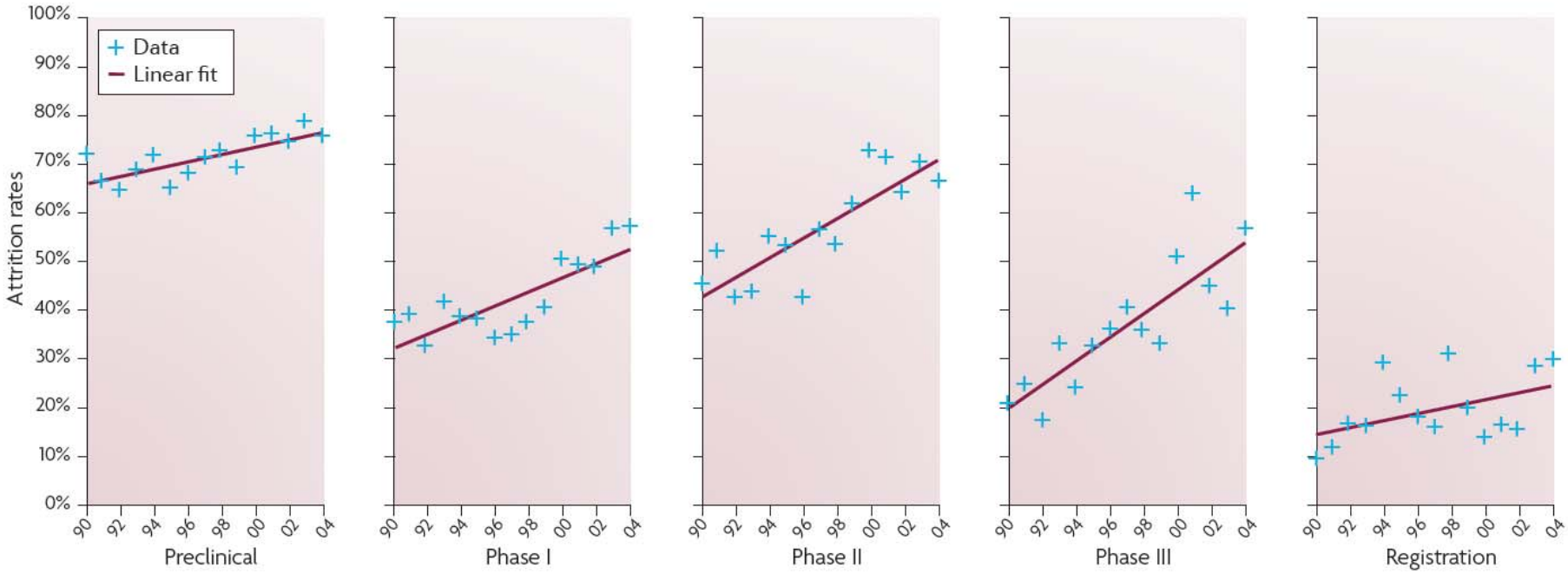


Despite Significantly Increased Spending, R&D Productivity has Declined



Source: Burril & Company, US Food and Drug Administration

Attrition Rates Have Increased at Each Stage of Development



Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov. 2011 Jun;10(6):428-38.

The Industry has been Targeting Investment in More Challenging Disease Areas

- Regression analysis:
  - Overall productivity: 0.48
    - Every year, the number of expected NMEs generated by the projects started between 2000–2004 is less than one-half of the number of expected NMEs per year generated by R&D projects started between 1990 and 1999
  - When “ATC” is taken into account, productivity is 0.92:
    - Within each disease category, productivity is constant
- The reduced output of pharmaceutical development appears to be driven by a change in the disease areas investigated

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Investment has Shifted to More Challenging Areas: Example, Oncology and CNS Disorders

Anatomical Therapeutic Classification (ATC1)	Number of projects	Average sales (US$ million)	Average POS (%)	Percentage of total projects		
				1990–1999	2000–2007	Change‡
L: Antineoplastic and immunomodulating agents	6,566	105.3	1.80	21.77	29.77	+8.00
Including L01: Antineoplastic agents	5,094	92.0	1.29	16.55	23.43	+6.88
N: Nervous system	3,817	43.5	2.85	14.46	15.55	+1.09
B: Blood and blood-forming organs	822	72.9	3.81	4.11	2.38	–1.73
J: Anti-infectives for systemic use	4,737	82.4	3.92	18.85	18.41	–0.44
M: Musculoskeletal system	1,472	22.6	4.19	6.49	5.10	–1.39
A: Alimentary tract and metabolism	2,046	14.8	4.46	7.26	8.82	+1.56
R: Respiratory system	1,165	13.3	4.81	5.07	4.10	–0.97
C: Cardiovascular system	2,139	45.6	4.86	10.72	6.15	–4.57
D: Dermatologicals	859	4.4	6.64	3.63	3.13	–0.50
G: Genitourinary system and sex hormones	865	21.0	11.75	3.95	2.86	–1.09
Other (H+P+S)§	945	11.2	19.79	3.70	3.73	+0.04

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HTA has been a Key Driver of this Shift

- Need to focus, in general, on areas of greatest unmet need
- Need to invest in programs that strengthen the demonstration/evidence of enhanced therapeutic value over standard of care (including head-to-head CTs)
- While a new treatment modality may have been sufficient for commercial success in the past, customers now looking for more substantial impact on patients/outcomes

What Data Do Payers Want to See?

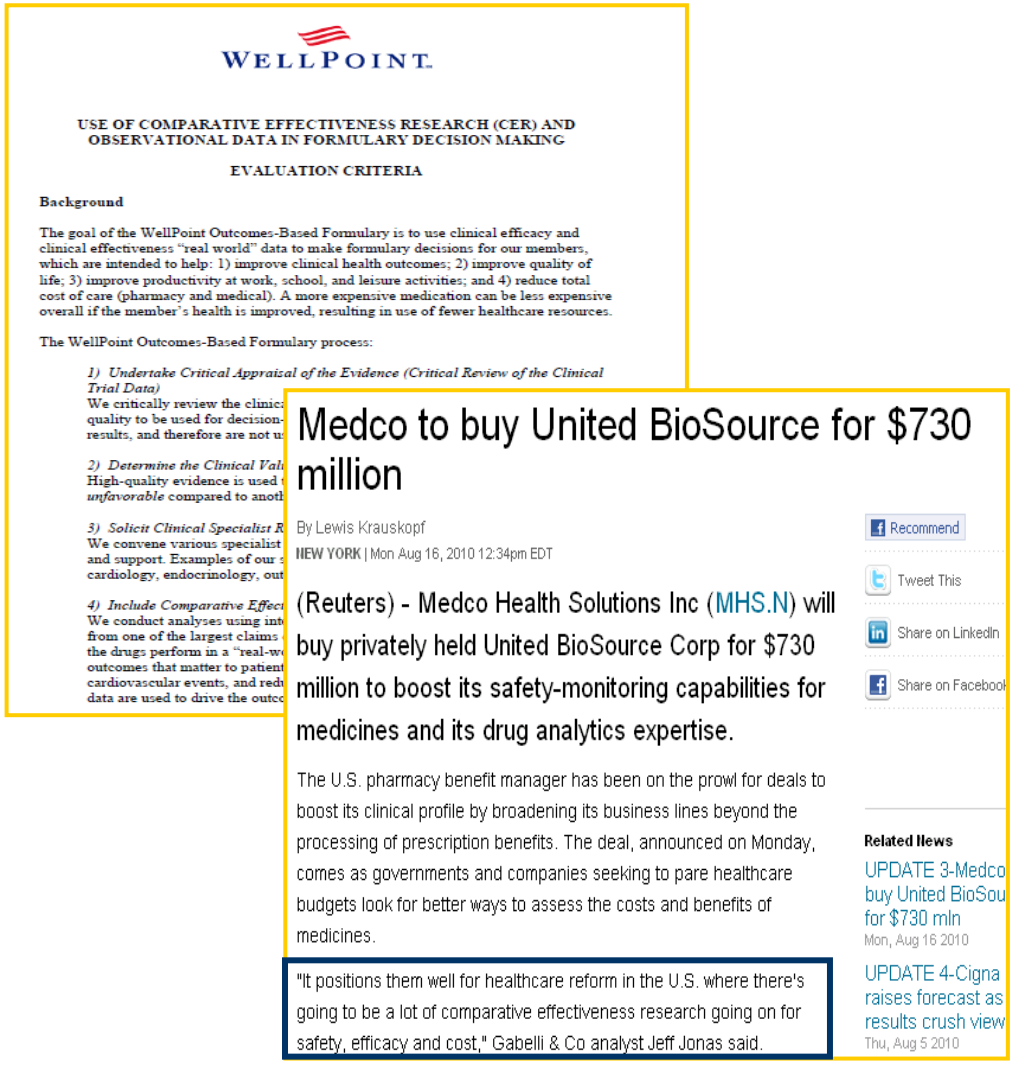
Comparative efficacy	▪ **Example, head-to-head trials (at least active controls)** ▪ **In exceptional cases, indirect or historical comparisons may be considered**
Final outcomes	▪ **Morbidity, mortality, patient *quality of life*** ▪ **Validated surrogate endpoints vs biomarkers and intermediate outcomes**
Real world conditions	▪ **Effectiveness vs. efficacy** ▪ **Data in patient populations in which drugs are used *in practice*, rather than populations studied in clinical development**
At the time of launch	▪ **May consider delaying access until greater experience accumulates *elsewhere*** ▪ **May assume other countries (eg US) will introduce drug, so might "wait and see" how it performs in routine care**

At Pfizer, HTA Considerations are an Integral Concern across the Product Life Cycle

POC/Phase II	• Incorporate HTA/payer insights into product “buy-up” and development strategies
Phase III, Registration, Launch	• Deliver compelling evidence package (Global Value Dossier) to satisfy the needs of regulators *and* payers
Life Cycle Management	• Optimize payer value proposition and evidence support throughout product life cycle

While HTA Was Primarily an Ex-US Phenomenon, the Market Place is Changing

- WellPoint Releases CER / OR guidance w/in a few months of PCORI notice
- Medco acquisition of United Biosource Corporation
- Wallgreens and Aetna build new internal outcomes research capabilities
- United Health has long standing outcomes research capability



WELLPOINT

USE OF COMPARATIVE EFFECTIVENESS RESEARCH (CER) AND OBSERVATIONAL DATA IN FORMULARY DECISION MAKING

EVALUATION CRITERIA

Background

The goal of the WellPoint Outcomes-Based Formulary is to use clinical efficacy and clinical effectiveness "real world" data to make formulary decisions for our members, which are intended to help: 1) improve clinical health outcomes; 2) improve quality of life; 3) improve productivity at work, school, and leisure activities; and 4) reduce total cost of care (pharmacy and medical). A more expensive medication can be less expensive overall if the member's health is improved, resulting in use of fewer healthcare resources.

The WellPoint Outcomes-Based Formulary process:

1) Undertake Critical Appraisal of the Evidence (Critical Review of the Clinical Trial Data)

2) Determine the Clinical Val

3) Solicit Clinical Specialist R

4) Include Comparative Effec

Medco to buy United BioSource for $730 million

By Lewis Krauskopf

NEW YORK | Mon Aug 16, 2010 12:34pm EDT

(Reuters) - Medco Health Solutions Inc (MHS.N) will buy privately held United BioSource Corp for $730 million to boost its safety-monitoring capabilities for medicines and its drug analytics expertise.

The U.S. pharmacy benefit manager has been on the prowl for deals to boost its clinical profile by broadening its business lines beyond the processing of prescription benefits. The deal, announced on Monday, comes as governments and companies seeking to pare healthcare budgets look for better ways to assess the costs and benefits of medicines.

"It positions them well for healthcare reform in the U.S. where there's going to be a lot of comparative effectiveness research going on for safety, efficacy and cost," Gabelli & Co analyst Jeff Jonas said.

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Mon, Aug 16 2010

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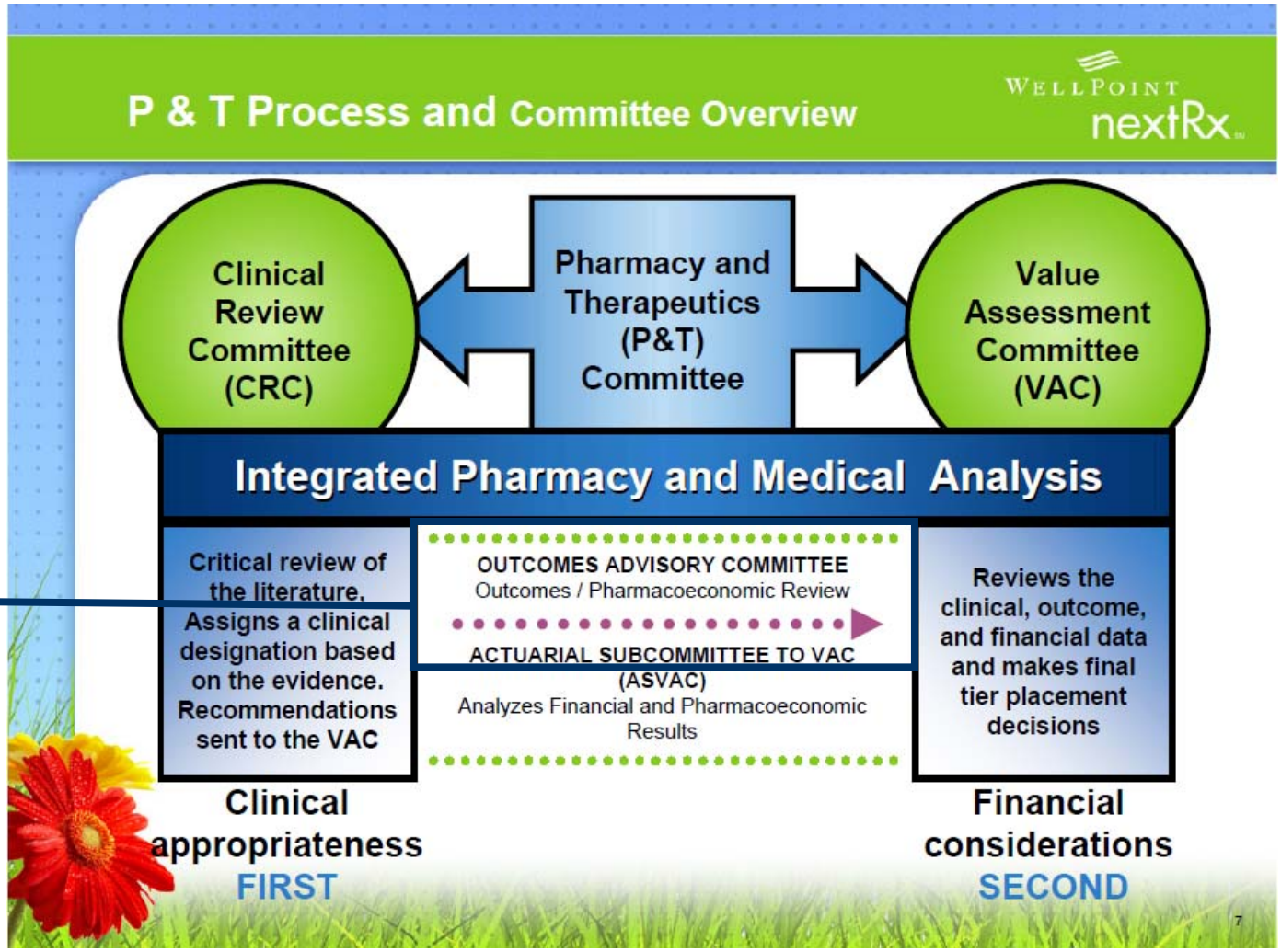
And US Payers are Implementing Similar Mechanisms for Formulary Decisions

- Lipitor versus Simvistatin analyses retains preferred 2nd Tier status
- Spiriva Vs. Combivent Vs. Others in COPD grants Spiriva favorable access
- Geodon Vs. Other Atypical Antipsychotics. Geodon remains at parity
- Lyrica Vs. Gaba Vs. Duoloxetine



How do We Ensure Input from HTA into Our Development Programs?

- In depth analysis of P&R systems and guidelines
- Systematic review of payer decision making and precedents
- Regulator and payer engagement for scientific and technical advice
  - Input incorporated into a medicine's development plan
- Standing payer advisory board
  - External validation of key assumptions and deliverables
- Payer & Pricing Research
  - Anonymous research conducted by an external agency

Adapting Our Model to Meet HTA Demands Requires a Predictable Environment that Rewards Innovation

- Pharmaceutical R&D remains a long term investment: ***We cannot adapt our clinical evidence programs to short-term changes in the HTA environment, eg in reaction to financial pressures***
- HTA continues to focus on new medicines: ***We need HTA to also focus on disinvestment of obsolete technologies to create headroom for innovation***
- We need a broad perspective on value: ***A mechanistic application of cost-effectiveness thresholds focused on direct medical cost is insufficient***
- Increasing price referencing of innovative products against generics creates market failure: ***We will increasingly acknowledge disease areas where the prices that can be achieved for new medicines will not justify the investment (infectious disease, hypertension, depression, even diabetes)***
- International price referencing undermines the global responsibility to finance R&D: ***We need a true value based pricing environment, based on evidence reviewed through HTA, where prices reflect the economic situation in the respective country***