Quantitative Risk/Benefit Assessment: Where are we?

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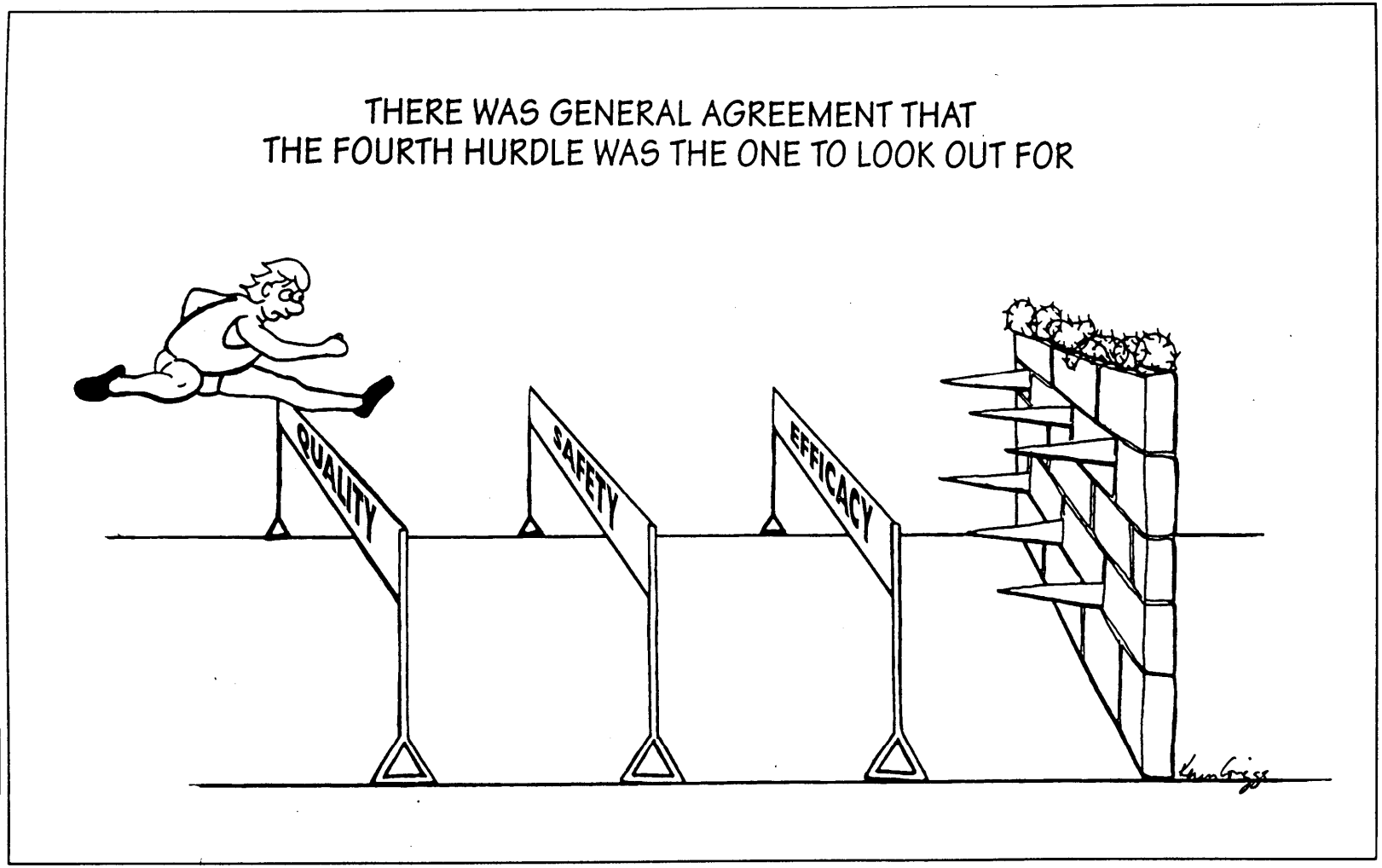
4th Seattle Symposium
November 23 2010

The Fourth Hurdle



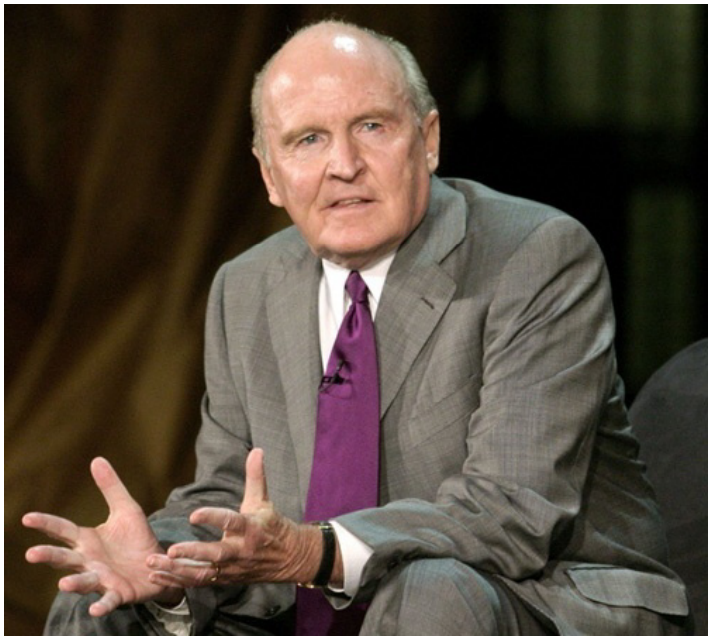
Source: Christoph Gerlingers

The Fourth Hurdle

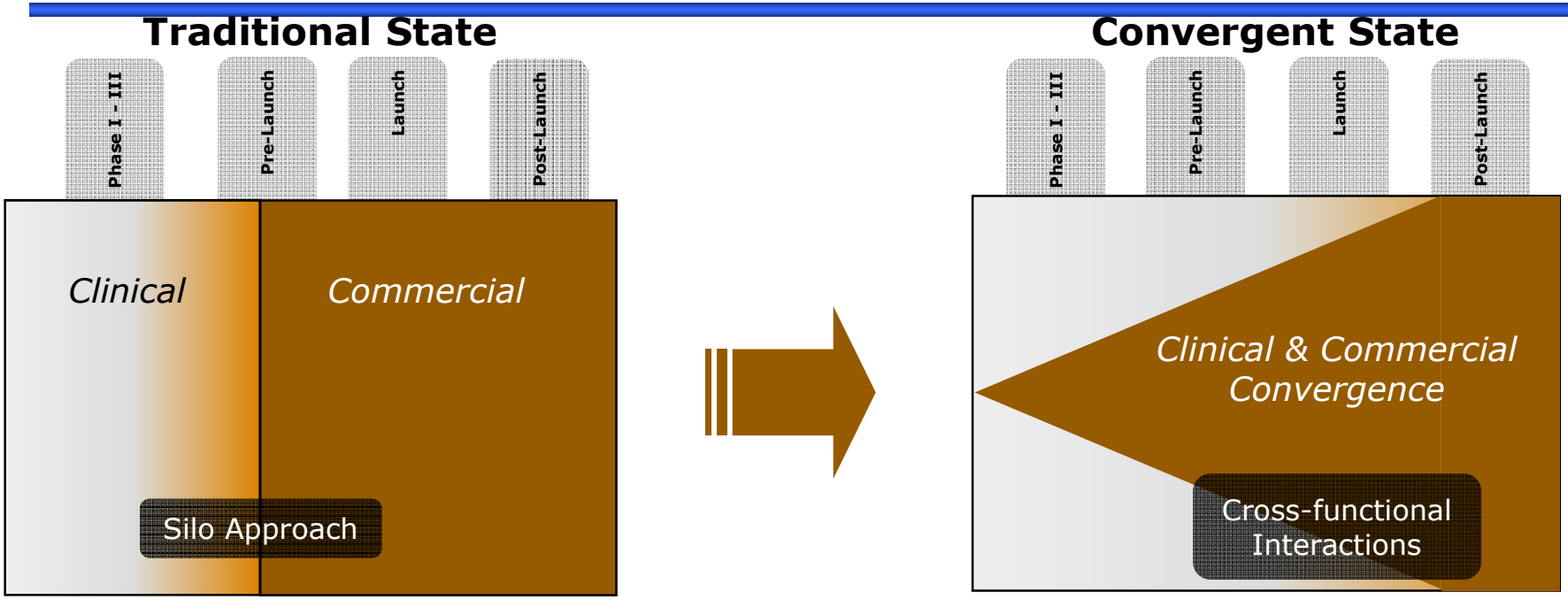
- Risk/Benefit?
- Relative Effectiveness?
- Comparative Effectiveness?
- Health Economics Evaluation?
- Health Technology Assessment?
- All of the above plus other emerging value propositions?

"When the rate of change internally is less than the rate of change externally, you are living on borrowed time."

- Jack Welch



An Evolving Operating Paradigm



Science driven - Efficacy and Safety	**Value Drivers**	HTA driven - Effectiveness and Efficiency
KOL input and *internal* medical perspective only	**Clinical Trial Design**	Expanded clinical input from a wider range of *external* stakeholders

New imperative: Integrating Market Access input early in clinical development to optimize value in the marketplace.

Source: Life Science Forum Basel / June 23, 2010 / FS (modified)

The Fourth Hurdle

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Recent FDA AC Product Reviews

- Nov 4: continuing use of IV phenytoin as an anti-seizure medication, or regulatory actions to diminish risks
- Oct 18: continuing use of Aranesp to treat anemia in patients with chronic renal failure not on dialysis
- Sept 20: dabigatran etexilate mesylate to prevent stroke in patients with atrial fibrillation
- Sept 16: naltrexone to treat opioid addiction
- **Sept 16: lorcaserin hydrochloride (with diet and exercise) for weight management for obese patients**
- Sept 15: continuing use of subutramine (Meridia) for weight management, after a cardiovascular outcomes trial

Lorcaserin, Sept 16 2010

- Endocrinologic and Metabolic Drugs AC
- Proposed indication: *Lorqess (lorcaserin) is indicated for weight loss and for maintenance of weight loss in patients with BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 and at least one weight-related comorbid condition.*
- The only question the AC was asked to vote
  - *Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals to allow marketing approval?*

At the AC Meeting

- There was general agreement that lorcaserin data met FDA efficacy criteria marginally.

- Issues and concerns
  - Lorcaserin is chemically similar to 2 weight-loss drugs (fenfluramine and dexfenfluramine, withdrawn in 1997) linked to left-sided valvular heart disease (VHD).
  - Lack data on interaction between lorcaserin and concomitant drugs known or suspected to carry risks for VHD.
  - Lack data in real-world patients with significant comorbid conditions (e.g. diabetes, hyperlipidemia, and CV disease).
  - 4 SAEs in the psychiatric SOC on lorcaserin, none in control.
  - 2-year studies in rats reported an excess number of malignant mammary tumors in female rats.

The AC Vote

Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals to allow marketing approval?

Vote Yes: 5

Vote No: 9

Outcome (October 22 2010)

- FDA rejected lorcaserin, signaling that safety concerns outweighed what the agency called the drug's marginal effectiveness.
- The biggest issue was that the drug in high doses (within 7-fold of the proposed clinical dose) caused tumor formation in rats.
- According to the sponsors, FDA asked for an independent review of the animal data and possibly new studies to establish that the animal findings were not relevant to people.

How Do We Make Decisions?

- A sensible approach seems to
  - Adopt a framework where all relevant information is captured.
  - Articulate the relative importance of various factors.
  - Identify a sensible way to quantitatively combine factors, taking into account their relative importance.
  - Check out the properties of the above and settle on a decision rule.
  - Identify conditions where a decision could be clear and unequivocal.
  - Make a decision and communicate it (and the process) to individuals who have an interest in the decision.

CUI in Early Development

The Use of a Clinical Utility Index to Compare Insomnia Compounds: A Quantitative Basis for Benefit–Risk Assessment

D Ouellet[1,2], J Werth[1], N Parekh[1], D Feltner[1], B McCarthy[1] and RL Lalonde[1]

The use of a clinical utility index (CUI) was proposed in order to compare two calcium channel α2δ ligands that were in development for the treatment of insomnia. The important attributes included in the CUI were two measures of residual sedation and five measures of efficacy (wake after sleep onset, sleep quality, sleep latency, and sleep stages (stage 1 and stages 3–4)). Dose–response analyses were conducted on each end point, and a sensitivity analysis was conducted to determine a clinically meaningful difference in CUI. Nonparametric bootstrap parameters were used to build confidence intervals (CIs). Peak CUI (80% CI) was 0.345 (0.25–0.43), observed at a dose of ~30 mg with the lead compound and 0.436 (0.35–0.52) observed at >600-mg dose for the backup. Although CUI was slightly greater for the backup, peak CUI values were observed at doses that were not considered viable, and therefore development of the ligand was discontinued. The use of the CUI allowed an efficient, quantitative, and transparent decision.

Source: Ouellet D, et al. Clin Pharmacol Ther 2009;85:277-82.

Normalizing and Weighting

Table 1 List of attributes, weights, and clinical differences used in the calculation of the CUI

	CUI—attribute	Clinical difference	Weight (%)
1	Residual effect (two measures from Leeds questionnaire)	5 points	35
2	Wake after sleep onset (min)	25 min	25
3	Quality of sleep	20 points	17
4	Latency to persistent sleep (min)	15 min	13
5	Sleep architecture (% in stage 1, % in stages 3–4)	5%	10

Source: Based on input from 581 physicians in the insomnia field. Ouellet D, et al. Clin Pharmacol Ther 2009;85:277-82.

PhRMA Benefit Risk Action Team

- Formed in 2006 with key objectives:
  - Formulate a framework for the ideal benefit-risk approach, including a methodology for integrating both qualitative and quantitative elements in an evolutionary way.
  - Provide greater structure and transparency for sponsor company - FDA alignment throughout approval process.
- BRAT partnered with RTI Health Solutions epidemiologists to complete the work in 2009.

PhRMA Benefit-Risk Framework

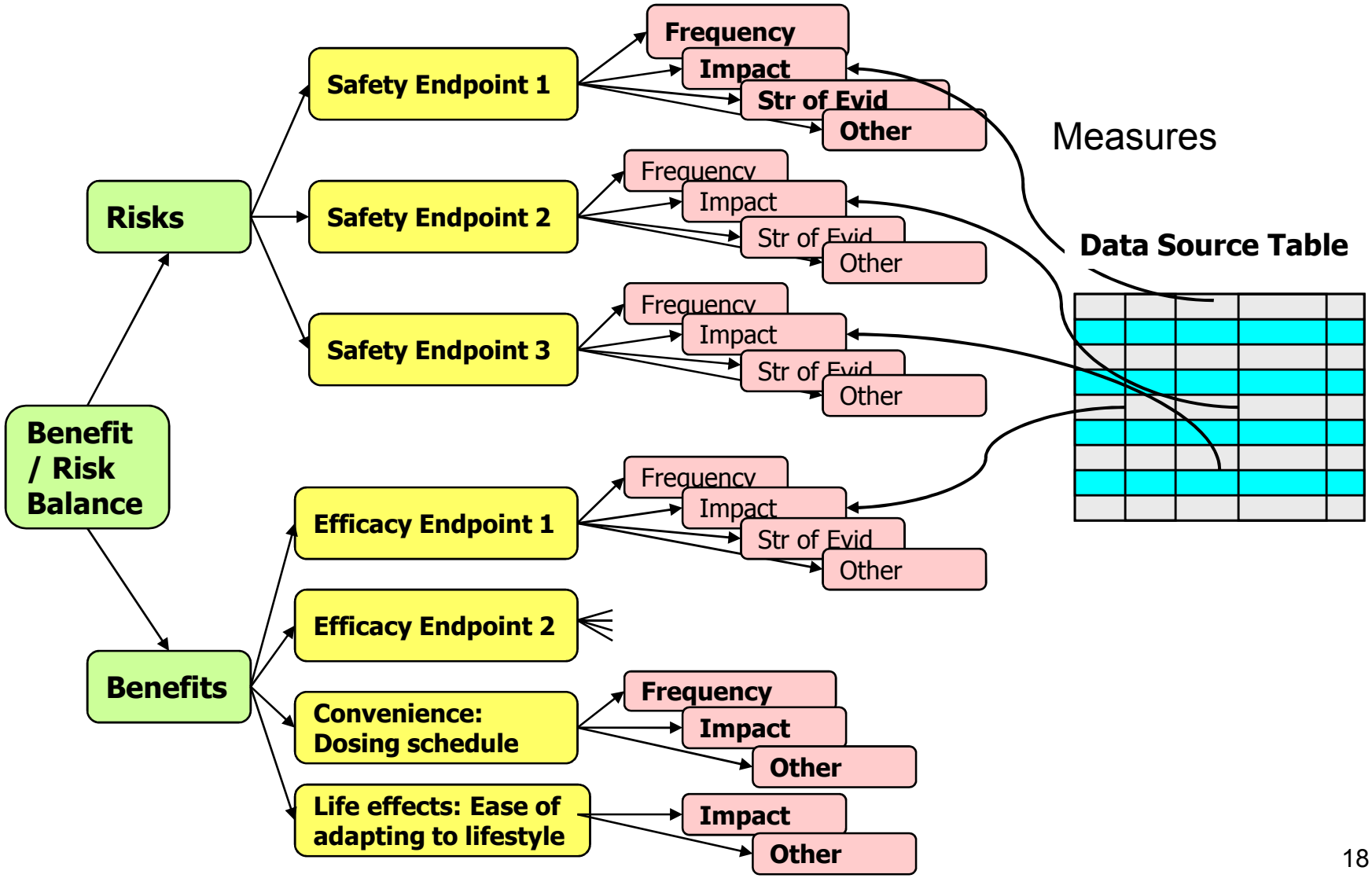
- The Vision
  - The framework can be considered a set of processes and tools to guide decision-makers in structuring, summarizing and interpreting the information.
  - Framework should be adaptable for different contexts depending on the type of information collected and structured, but the fundamental of the framework remains the same.
- The Work
  - There were 3 rounds of development and testing (statins, tumor necrosis factor – alpha antagonists, and triptans), using mock products in different therapeutic categories.

Envisioned Steps of Framework

- Establish the Decision Frame.
- Identify the Benefit and Risk Outcomes (selections and definitions)
- Choose the Metrics - the specific measurements to quantify benefit and risk outcomes
- Identify and Organize the Data Source
- Adapt the Value Tree, Data Source and Summary Tables
- Calculate the Metrics – apply weights where applicable for quantitative assessment
- Interprete the Assessment – visualization method or approach

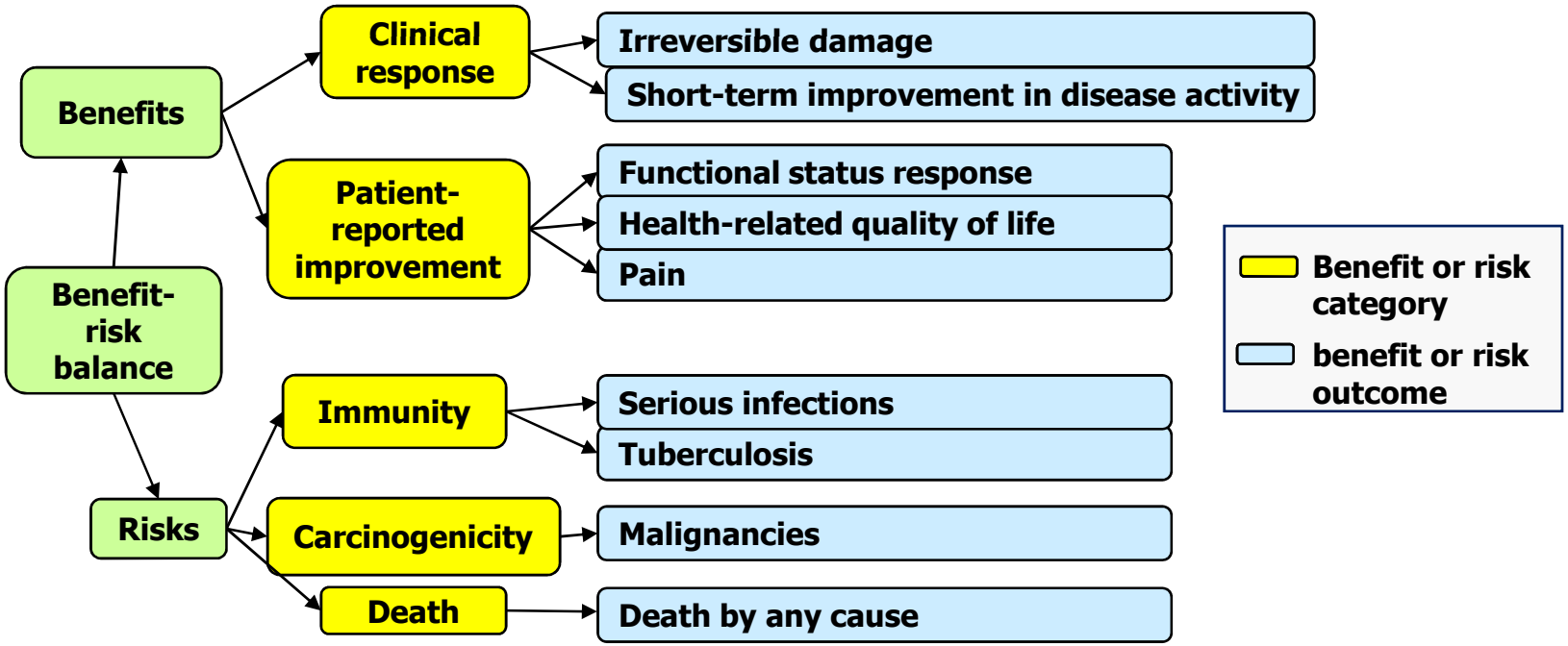
Source: PhRMA BRAT Framework Project Round 2 (slides 17 - 21), 8 March 2010

Framework Process



TNF- α Blockers for Rheumatoid Arthritis

- Repeated tuning led to the following framework.
- Solid malignancies, lymphoproliferative cancers, and non-melanoma skin cancers combined into one category "malignancies"

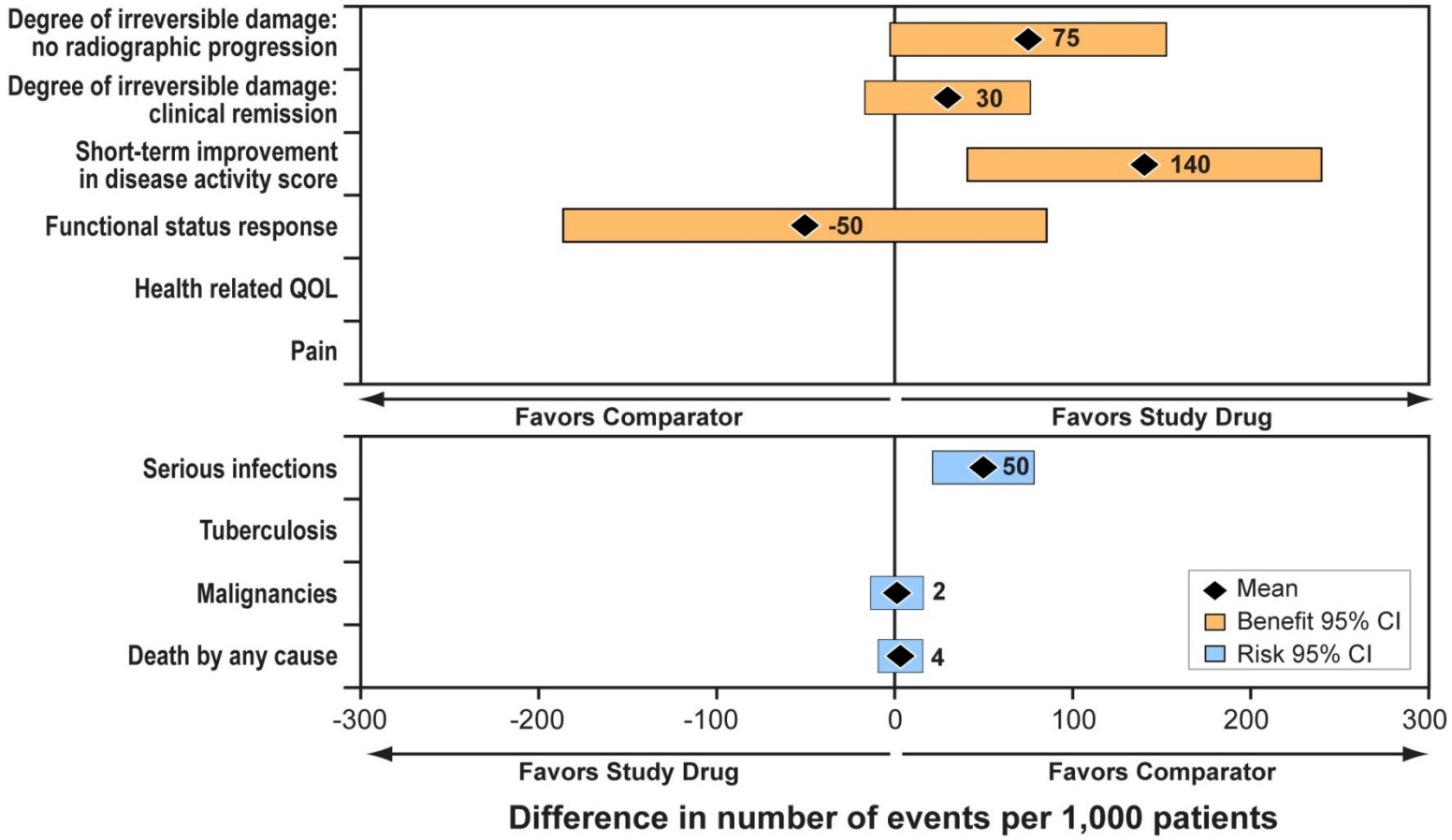


Key Benefit-Risk Summary Table

		Outcome	Outcome Measure	Study Drug (%)	Active Comparator (%)
Benefit	Clinical response	Degree of irreversible damage	No radiographic progression (change in Sharp score < 0.5)	39.2	31.8
			Clinical remission (DAS < 1.6 or DAS28 < 2.6)	14.0	10.9
		Short-term improvement in disease activity score	ACR-20 response at 14 weeks	51.9	37.9
	Patient-reported improvement	Functional status response	HAQ-DI clinically meaningful improvement (≥ 0.22 units)	58.0	63.0
Risks	Immunity	Serious infections	Proportion of patients	10.5	5.5
		Tuberculosis	Proportion of patients	0.0	0.0
	Malignancies	Malignancies	Proportion of patients	1.4	1.2
	Death	All cause death	Proportion of patients	0.7	0.2

Difference in # of Events per 1,000 Patients

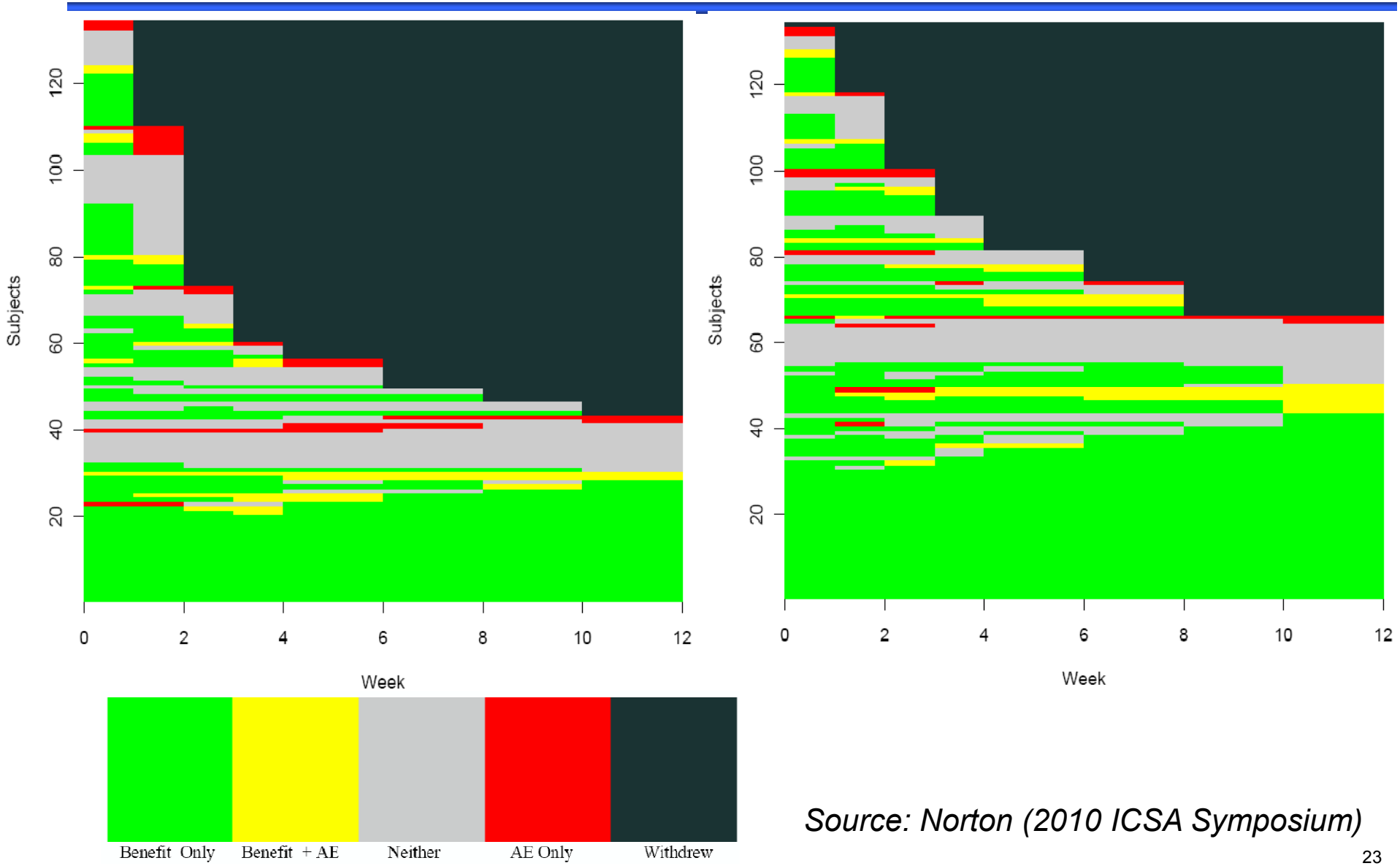
- Graphical displays help with interpretation of data
- There are 2 different axes for Benefit and Risk data on this version (Benefit= positive outcome, Risk = negative outcome)



Benefit/risk Measures

- Benefit/risk ratio
  - Ratio of (*number needed to harm)* and (*number needed to benefit)*
- Combined index
  - Unweighted and weighted indices
- Global benefit-risk measure
  - Joint distribution of desirable and undesirable outcomes
  - Linear and ratio scores
- Risk-adjusted benefit measure
  - Qualify-adjusted life; benefit discounted by risk

Joint Outcomes: Control (L), Drug (R)



Source: Norton (2010 ICSA Symposium)

Prescription Drug Facts: AMCID (amoditine)

What is this drug for?	To relieve heartburn
Who might consider taking it?	Men and women bothered by heartburn or acid reflux disease
Who should NOT take it?	Women who are pregnant or breastfeeding
Recommended testing	None
Other things to consider doing	Eat frequent small meals; avoid fatty foods (and others which trigger your symptoms); excessive alcohol and eating close to bedtime; don't smoke; look into other medications.

AMCID Study Findings Box

500 people with bothersome heartburn were given AMCID or a sugar pill for 2 weeks. Here's what happened:

What difference did AMCID make?	People given a sugar pill	People given AMCID (20 mg a day)
Did AMCID help? Fewer people taking AMCID had heartburn (17% fewer)	81% 810 in 1000	64% 640 in 1000
Did AMCID have side effects? *Life threatening side effects* No difference between AMCID and a sugar pill	None observed	
Symptom side effects No difference in headache	About 5% in both groups 50 in 1000	
No difference in diarrhea	About 2% in both groups 20 in 1000	
No difference in dizziness	About 1% in both groups 10 in 1000	

How long has the drug been in use?

Amcid was approved by FDA in 1991 - Studies show that most serious side effects or recalls of new drugs happen during their first 5 years of approval.

Wolosin and Schwartz
Drug Facts Box

FDA Risk Communication
Advisory Committee Meeting

Feb 26-27, 2009

HR 3590: Health Care Bill

- ***(a)*** *IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as the "Secretary"), … shall determine whether the addition of quantitative summaries of the benefits and risks of prescription drugs in a standardized format (such as a table or drug facts box) to the promotional labeling or print advertising of such drugs would improve health care decisionmaking by clinicians and patients and consumers.*

- ***(d)*** *If the Secretary determines … that the addition of quantitative summaries … in a standardized format (such as a table or drug facts box) … would improve health care decisionmaking …, then the Secretary, not later than 3 years after the date of submission of the report …, shall promulgate proposed regulations as necessary to implement such format.*

Acknowledgement: Jon Norton, CDER/FDA

EMA: Benefit-risk Methodology Project

- Issued a (work package 2) report on "*Applicability of current tools and processes for regulatory benefit-risk assessment*", August 31 2010.
- The report describes a generic qualitative approach of 8 steps and 18 quantitative approaches; also describes work in progress by PhRMA BRAT, CMR CASS (Canada, Australia, Swiss and Singapore regulators) study, and FDA BRF (benefit-risk framework).
- It acknowledges that any quantitative method or approach requires a qualitative framework within which the model could be effectively developed.
- Combinations of approaches will prove useful on many situations.

Risk/Benefit Assessment: Where are we?

- We have seen some applications at FDA meetings (e.g. Feb 3 2009 FDA Cardio & Renal AC meeting).
- FDA Drug Safety & Risk Management AC meets regularly to review most-marketing safety data.
- Many questions remain
  - How do we assess conflicting results from meta analyses on a marketed product?
  - Whose risk/benefit should we consider? How do we communicate to stakeholders in an understandable way?
  - Can we have transparency without quantification?

How Can Statisticians Help?

- Statistical engineering
  - The study of how to best utilize statistical concepts, methods, and tools and integrate them with information technology and other relevant sciences to generate improved results (Hoerl and Snee, *Quality Progress*, May 2010)
  - Trying to build something with the statistical science parts list
- Statistical engineering can be applied to improving anything.
- It could help with risk/benefit assessment also.

Source: Roger Hoerl and Ron Snee, JSM 2010 (modified)

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