The Future of Drug Safety
An Insiders View

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These are my views not necessarily those of companies that I am or have been affiliated with.
The future of safety is …

very different
The Essence of Safety

“It’s all about the people.” *

* Gerry Faich
“Reputation is Everything” *Ψ

• PricewaterhouseCoopers surveys:
  – risk to reputation:
    • closely linked to financial health
    • the risk with greatest market impact
    • key threat to business growth (40% of CEOs)

• Research Institute analysis:
  – 5% ↓ reputation → 5% ↓ market value

Ψ “Risk, Value, and Reputation,” by Dr. Charles J. Fombrun, Executive Director, Research Institute, presented in Singapore on December 2, 2004.

* Recapturing the vision* Restoring trust in the pharmaceutical industry by translating expectations into actions PricewaterhouseCoopers’ Health Research Institute
The Future of Product Safety will be determined by the manner in which industry addresses key asymmetries.
Efficacy-Safety Asymmetry

A rational motivation for change
Benefit-Risk Asymmetry

A rational motivation for change
Key Asymmetries

• funding - of safety vs. efficacy
• relationships - governance structure for safety vs. efficacy
• science - safety vs. efficacy
• communication - the value of medicines
Funding of safety vs. efficacy

Rationalize the ~ 50:1 ratio for Clinical Development : Clinical Safety
Command Structure
safety vs. efficacy

• corporate standing – Chief Safety Officer (CSO)
• equal partner in life-cycle decision-making
• centralized control of fully integrated function
• support functions similar to clinical development
• risk-based model
Command Structure
safety vs. efficacy

• closely linked to Corporate Risk Management
• explicit top management support (leverage “with teeth”)
• heavy investment in:
  – people
  – communication framework
  – training systems
  – technology optimization
Beyond the Horizon

CEO

CMO
Chief Medical Officer

CSO
Chief Safety Officer
Science of Safety & Efficacy

• state-of-the-art - measuring safety
• pre-approval safety
• active surveillance
• life-cycle risk management
• benefit-risk optimization
State-of-the-art

“We don’t know how to measure safety”*

Asymmetry:

• ‘metrics of benefit’ & ‘metrics of harm’
• capacity to evaluate safety vs. efficacy at all stages in product development
• must be addressed before we attain a ‘Science of Safety’

* Regulator to remain unnamed
The problem goes beyond the ‘metrics of harm’ …
We need more systematic agreement on the ‘burden of proof’

- it’s all about causality
- causality paradigms are fundamentally weaker for safety than and than for efficacy (very few exceptions)
- in general, there is no choice but to accept a lower level-of-evidence for safety-related decision-making, and …
- progress requires:
  - agreeing on a scale of level-of-evidence for harm (perhaps analogous to those for efficacy)
  - systematically linking level-of-evidence to regulatory action
- in passing, the same is true for effectiveness and comparative effectiveness research
Risk Conditioned on Benefit
The Mother of All Asymmetries
## Risk Management Guidances

<table>
<thead>
<tr>
<th>Framework for Risk Management</th>
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<tr>
<td>Need to balance benefit &amp; risk</td>
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<td>Framework for balancing benefit &amp; risk</td>
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<td>Guidance on balancing benefit &amp; risk</td>
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Benefit & Risk (BR)
Two Sides of the Same Coin

We accept the possibility of harms in return for the possible benefits that outweigh them.
Risk Management

What happening to benefit?

Balance is changing

… but not at the expense of risk
State-of-the-Art
Benefit-Risk
Today’s BR Balance

A heuristic approach to decision-making

• educated impression
• based on implicit probabilities & values
• inscrutable, subjective, piecemeal, integration & weighting of evidence that is not standardized or reproducible
Regulatory Implications

Subjectivity may contribute to different actions across regulatory jurisdictions
Benefit-Risk ‘String Theory’

- outcomes
- probabilities
- values (perceptions)

(outcome probability values)

(Benefit\textsubscript{1} Benefit\textsubscript{2} Benefit\textsubscript{n} (composite benefit))

(Risk\textsubscript{1} Risk\textsubscript{2} Risk\textsubscript{n} (composite risk))
Common Scale

Apples & Cranberries → Cran-Apple

risks

benefits

common scale
Decision Framework
A working Definition

A system used to coordinate a collective thought process, carefully managed to clearly delineate a meaningful and tractable problem, in unambiguous and actionable terms, leading to explicit decisions that can be measured, revisited and revised.
Need for Structure in Decision-Making

Framework vs. Quantitative Model

Increasing Decision Complexity/Importance

Increasing Need

Decision Framework

Quantitative Model
There is Quantitative then there’s …

A word of caution

• annual Bangladesh butter production over 13-years *
• model "explained" 75% of variation in S&P 500 index annual returns
• adding U.S. cheese production & total # of sheep in Bangladesh & U.S "predicted" past U.S. stock returns with 99% accuracy
• then there’s the academic cardiologist who …

* WSJ - Leinweber
So what are we doing about the Science of Safety it?
The Players

Academia

Regulators ——— Industry
Examples

• Re-engineering Product Development
  – MIT Center for Biomedical Innovation (CBI)
  – Gigi Hirsch & colleagues

• Active Surveillance
  – Vaccine and Medication in Pregnancy Safety Surveillance (VAMPSS)
  – Allen Mitchell & colleagues
Center for Biomedical Innovation
MIT-CBI

- re-engineering product development, to get right products, to right people at right time more efficiently
- consortium launch 2009
- systems approach to optimizing cross-stakeholder value
- leveraging MIT experience gained in transforming other industries
Center for Biomedical Innovation
MIT-CBI

• stakeholders include: pharmas, a biotech, a CRO, FDA, NIH, AHRQ, Brookings and MIT and Harvard faculty

• considerations include modulation of innovation by regulatory/statutory constraints and stakeholder risk tolerance

• in very early stages!
Vaccine And Medication in Pregnancy Safety Surveillance (VAMPSS)

• endorsed by CDC and FDA
• established academic researchers coordinated by the American Academy of Allergy Asthma and Immunology
• 2 complementary data collection designs
  – prospective cohort design by Organization of Teratology Information Specialists (OTIS)
  – case-control provided by Slone Epidemiology Center (SEC) Birth Defects Study at Boston University
• full range of outcomes
• adjusted analyses
Vaccine And Medication in Pregnancy Safety Surveillance (VAMPSS)

• standing Independent Advisory Committee
  – biostatistician, a reproductive epidemiologist, a consumer representative, and representatives from CDC, NICHD, NHLBI, NIAID, ACOG, and AAP

• analysis focuses on 2 concepts
  – safety threshold: level-of-evidence supports absence of risk
  – risk threshold: possible signal that warrants evaluation

• Advisory Committee determines whether the evidence reaches the threshold criteria & may recommend labeling
Asymmetry in Communication
The value of medicines

Unopposed risk communication??
On the Pace of Change

If the automobile had followed the same development cycle as the computer, a Rolls-Royce would today cost $100, get a million miles per gallon, and explode once a year, killing everyone inside.*


* Robert X. Cringely
“Keep it as simple as possible and no simpler” *

* Albert Einstein