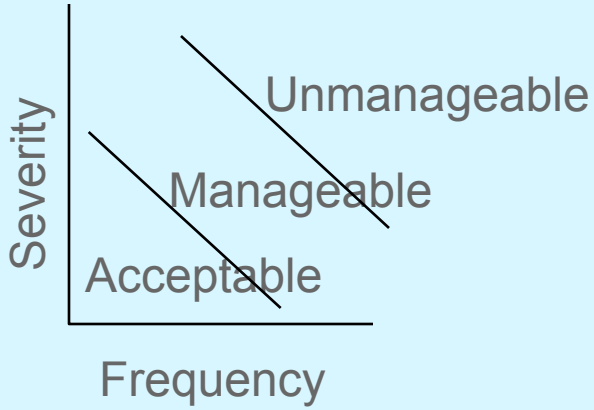
Joint Industry / FDA Symposium
Managing Risks – From Pipeline to Patient
Track 4 – Drug and Device Development and Clinical Trials

A Cross-Functional Perspective of Key Issues Facing New Product Introductions



Claudio Pincus
Owen Richards
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Harvard University

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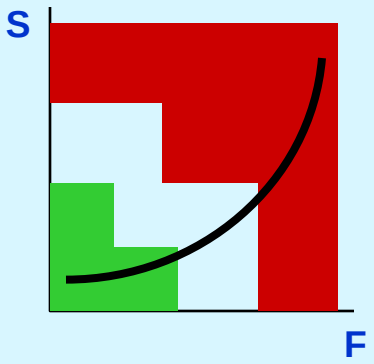

The Quantic Group℠

The Quantic Group, Ltd., Livingston, NJ

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R&D is decision-making at risk

The world of pharmaceutical R&D succeeds or fails based on risk decisions over time by multiple stakeholders

Pharmaceutical R&D requires frequent decision making at risk

- Pursue or abandon drug candidates
- Decide on Scientific path
- Project acceleration
- Interpretation of Regulatory Requirements
- Design of Protocols
- Design safety programs

To optimize results and use resources

- First to market
- Shortest time
- Optimize investment
- Fit to core strategy
- Maximum return
- Right the first time approval

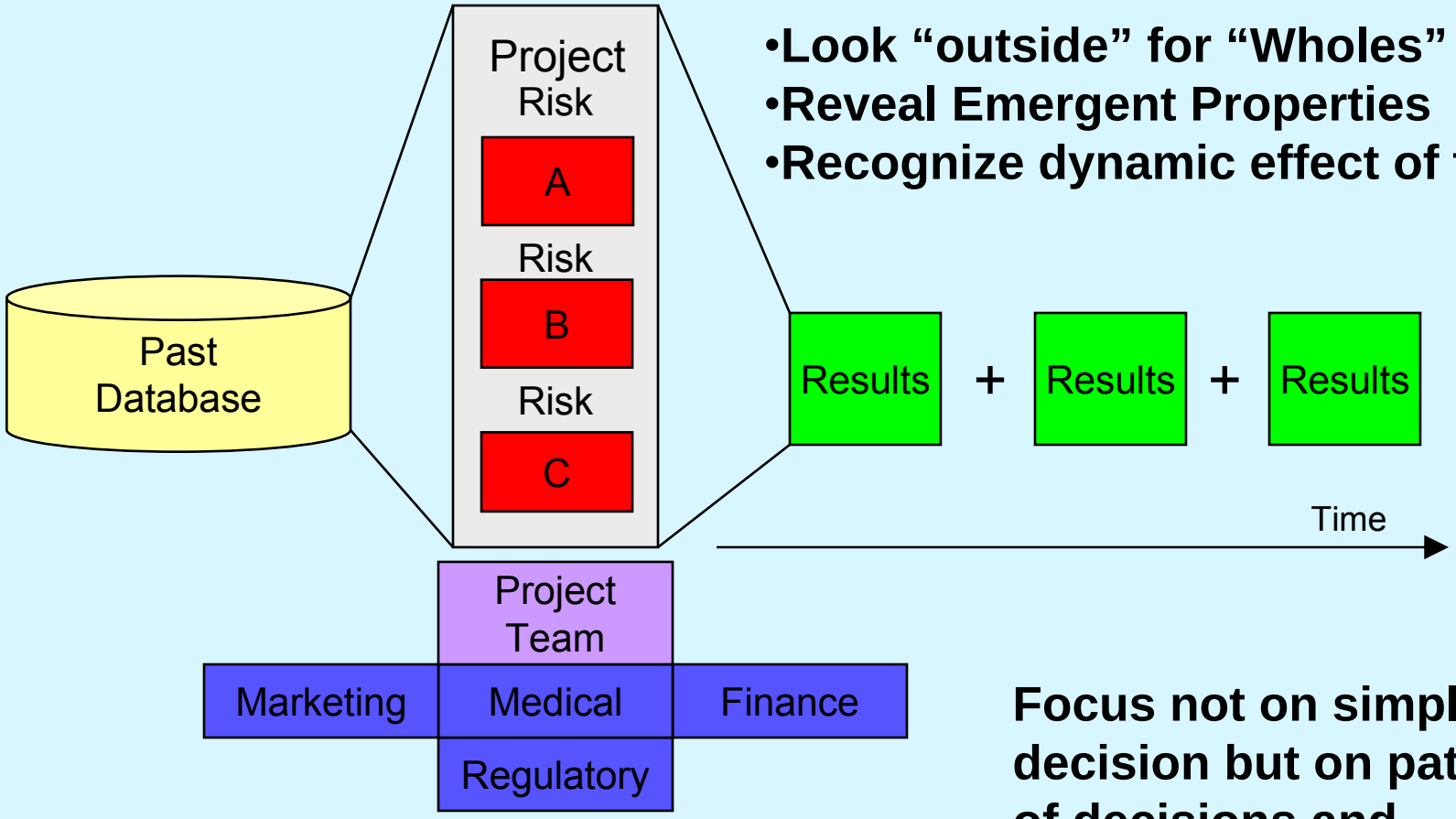
There are positive consequences

Risk decisions can result in positive or negative results

Negative	Positive
Have consequences that can be predicted	Provides an opportunity for extraordinary gain
- Study failure	+ Major breakthrough
- Non-approval	+ First to Market
- Regulatory action	+ Blockbuster
- Project Cancellation	
- Financial Loss	
- Product liability	

Without risk analysis, decisions are made without an informed management process

Systems thinking helps risk decision-making



- **Look "outside" for "Wholes"**
- **Reveal Emergent Properties**
- **Recognize dynamic effect of time**

Focus not on simple risk decision but on patterns of decisions and relationships among decision makers

Systems thinking is a framework for seeing interrelationships rather than things

Static Properties	Versus	**Dynamic Relationships**
•What they are •How they are composed		•How things connect and affect each other

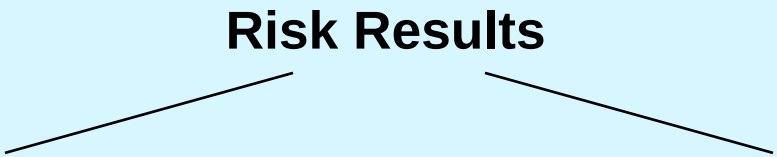
Observe patterns of change rather than static snapshots

The systemic view of Risk allows for negative and positive results

The result is represented by the "two sides of the coin."

Definitions of Risk:

- **Performance variance**
- **The potential for adverse impact of uncertainty on decisions**
- **The possibility that something will go wrong to prevent the achievement of specific business objectives**
- **The possibility of loss, injury, disadvantage or destruction**



Negative
- Failures
- Loss

Positive
+ Learning
+ Rewards
+ Opportunities

The Systems View

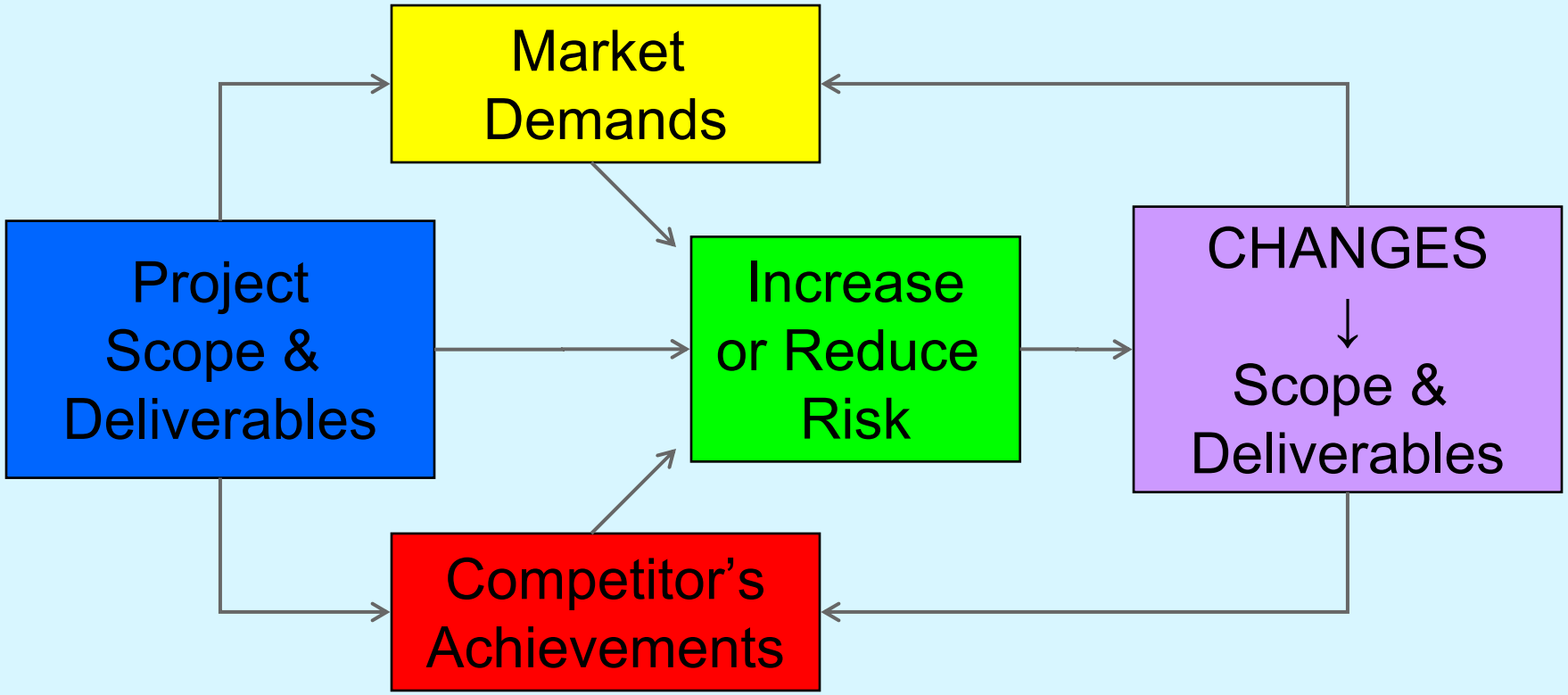
"Our unit of analysis is not
the single risk decision decomposed
into the details of how it is made,
but aggregates of decisions
over time or across programs,
to see patterns or trends.

Our attention is focused not on individual decision-makers, but on the relationships among decision makers, or between individuals and the teams, departments, and companies of which they are a part"

Singer, "Systems Thinking and the Risky Business of Clinical Supplies", pg. 42; PharmEngineering, Sept 2002

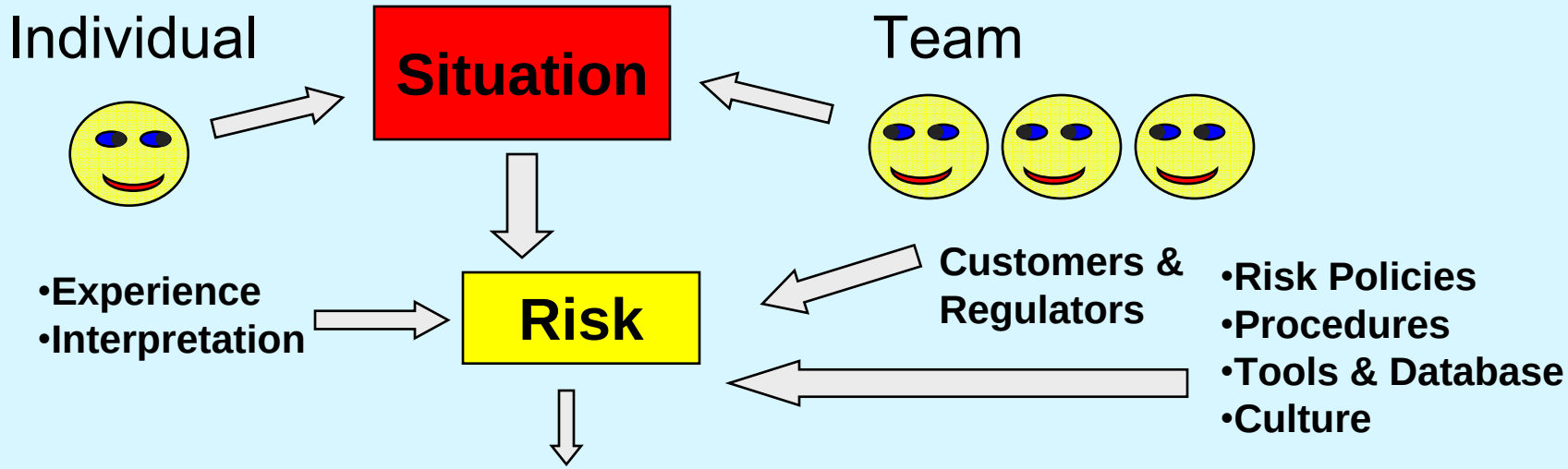
Successful R&D Depends on Wholes and on Knowledge of the Implications of Risk

Success in R&D requires a constant evaluation of the internal and external forces of changes and the necessary action to overcome adversity



Individual decision making tends to be risk averse

Empowered teams with risk policy, guidelines and tools foster learning and better risk based decision making



-One at a time
-Neglect the past
-Miss the opportunity

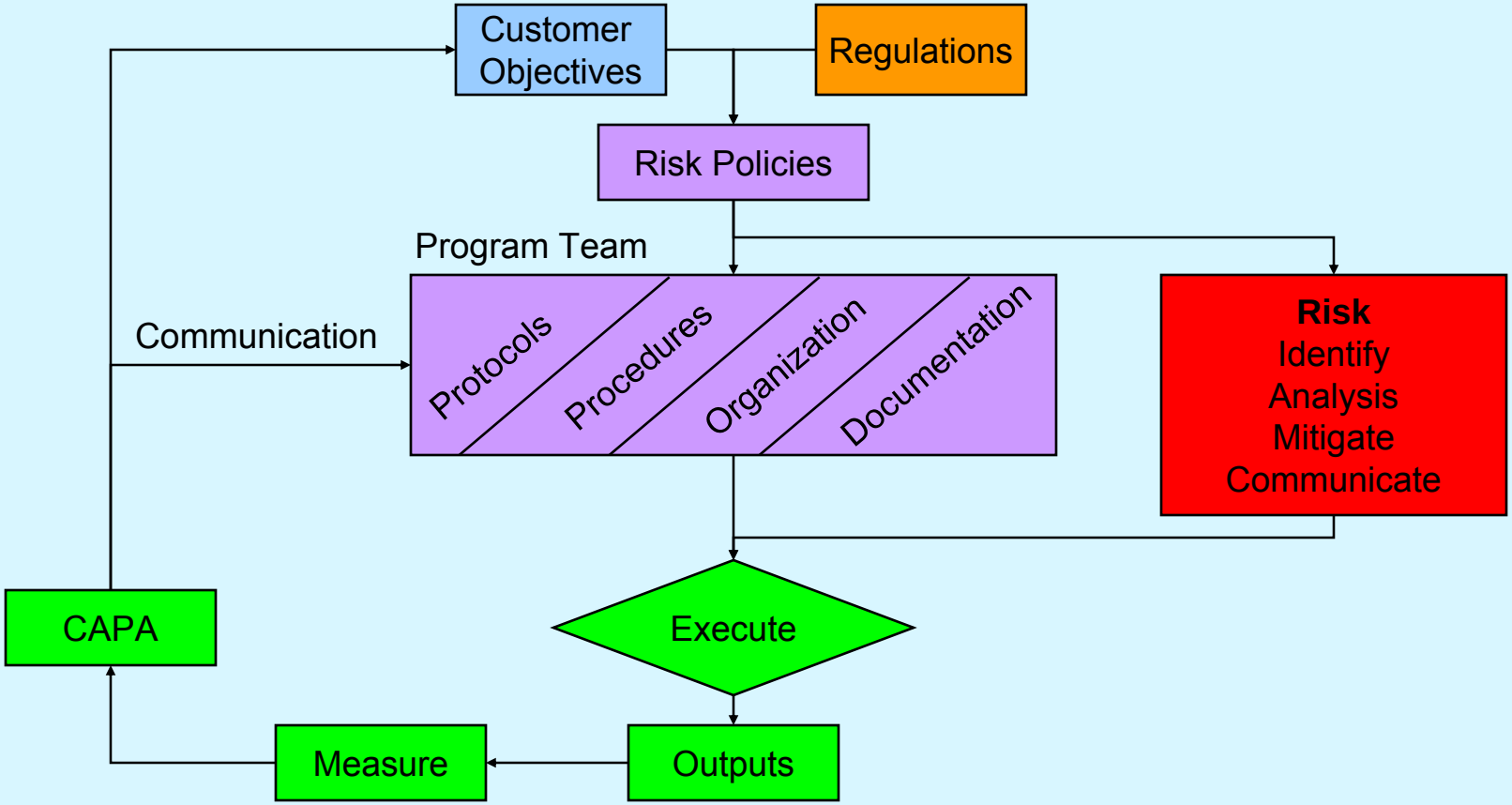
Becomes Risk averse Over time

+Shared Risk Understanding
+Best practices
+Adapts to circumstance

More likely to meet company risk tolerance goals

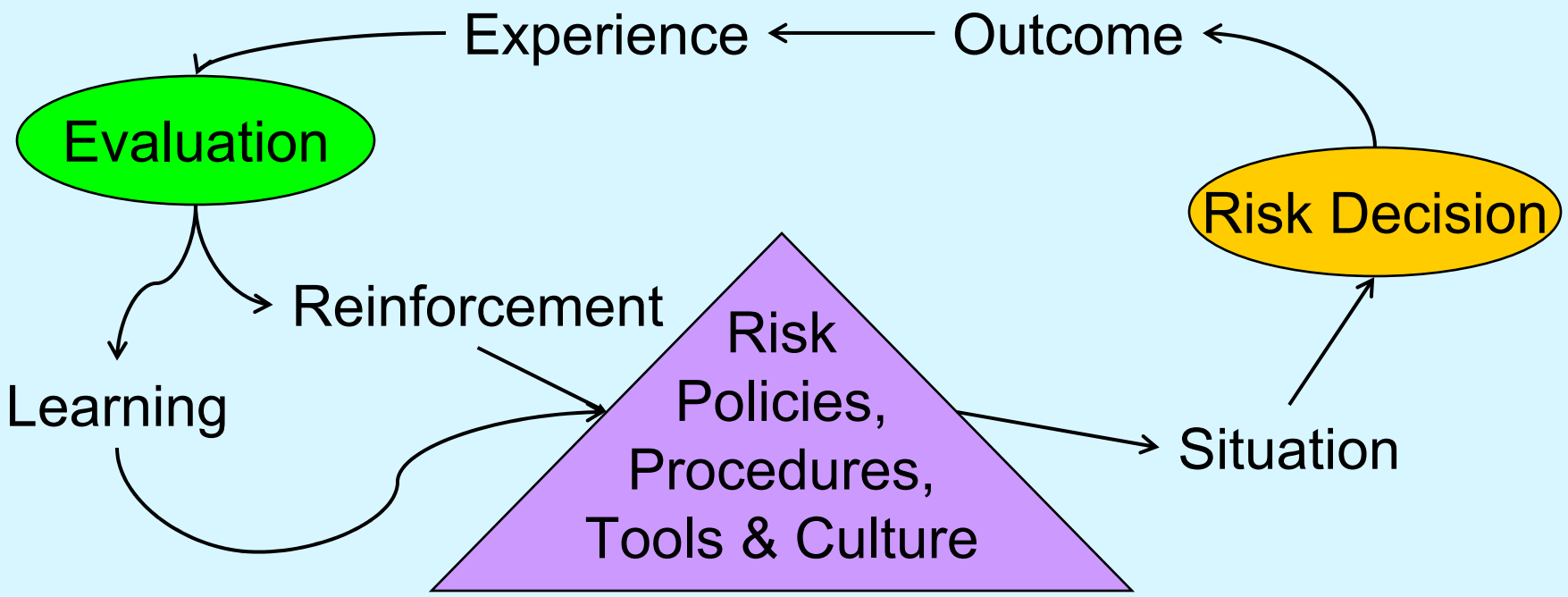
Central to system thinking is the feedback concept

Compliance with customer objectives and regulations is the organizational capability to predictably and consistently prevent, detect and correct deficiencies based on risk considerations



Risk tolerance is best defined, learned and implemented through the combined team experience

Each risk decision provides experience for the collective knowledge base, but the information must be understood in terms of its singular circumstance



Adapted from Singer, "Systems Thinking and the Risky Business of Clinical Supplies", pg. 42; PharmEngineering, Sept 2002

In summary . . . Risk management

Involves a systemic approach to apply process and knowledge to produce better outcomes

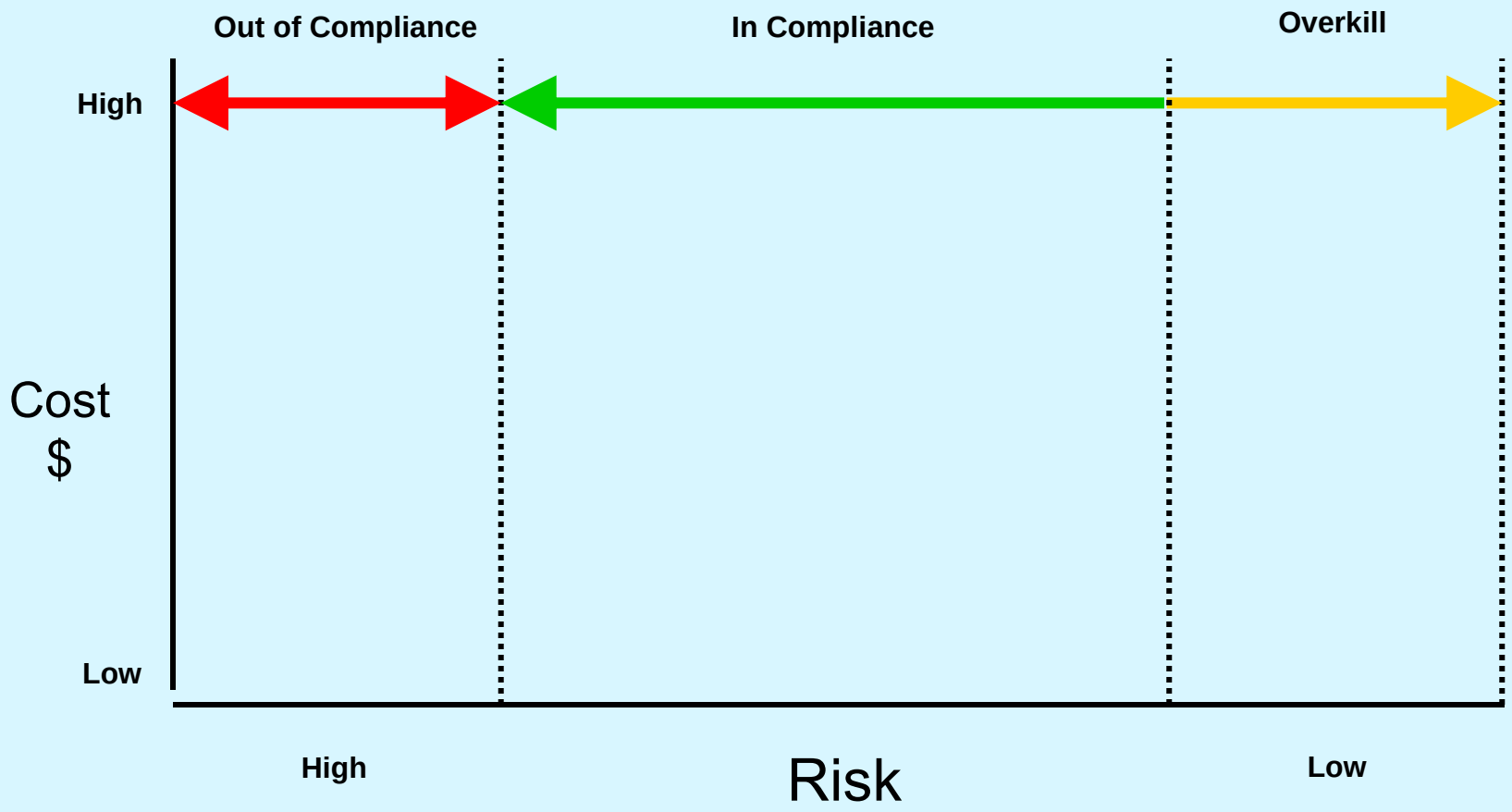
Recognizes

- **Risk opportunity**
- **Interrelationships**
- **Holistic nature**
- **Dynamic process**
- **Self-improving processes**
- **External components are involved**
- **Repeatable processes**
- **Group decision processes**

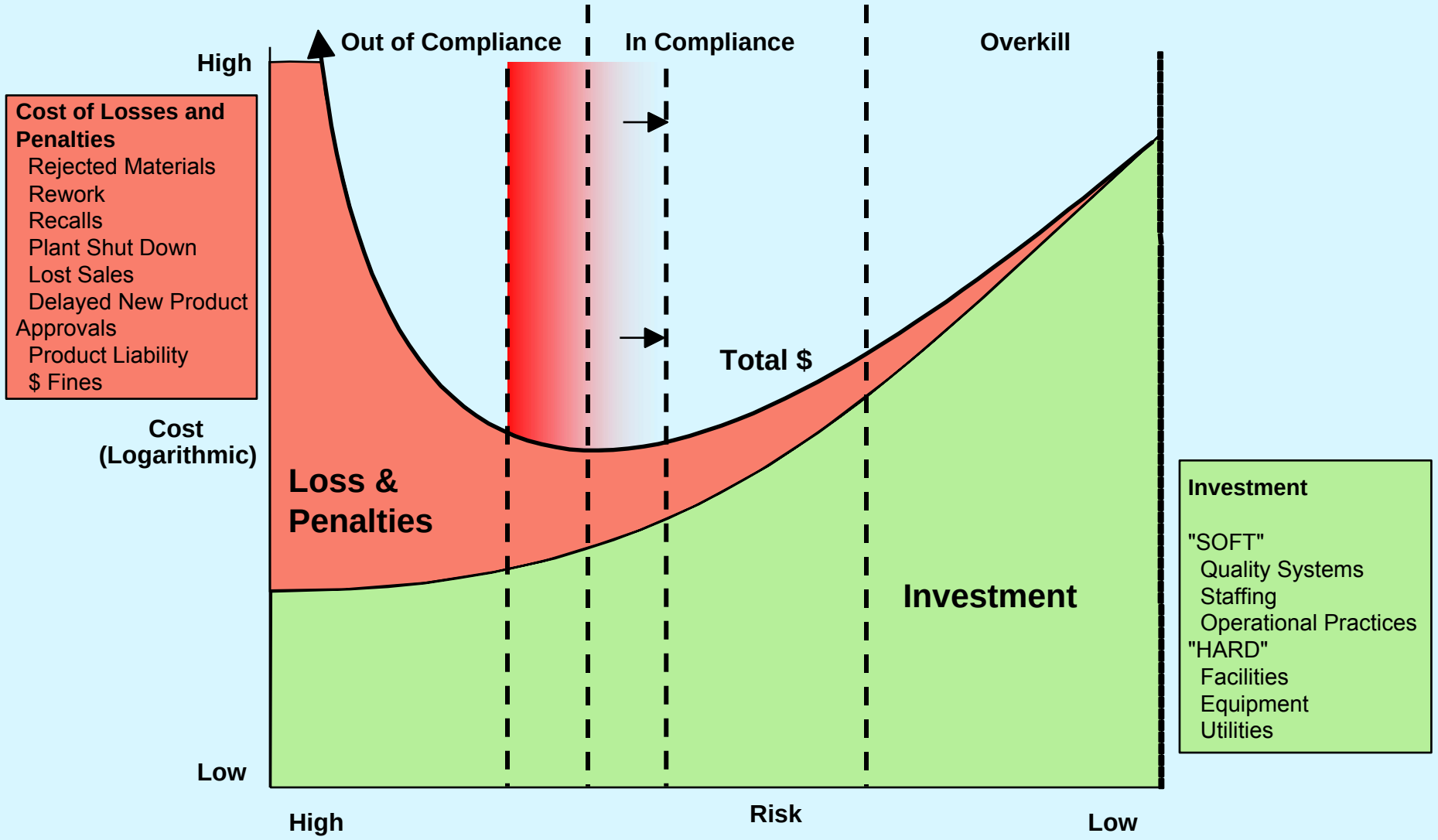
Risk is an assessed loss potential

Risk = Probability x Severity X (Detectability)

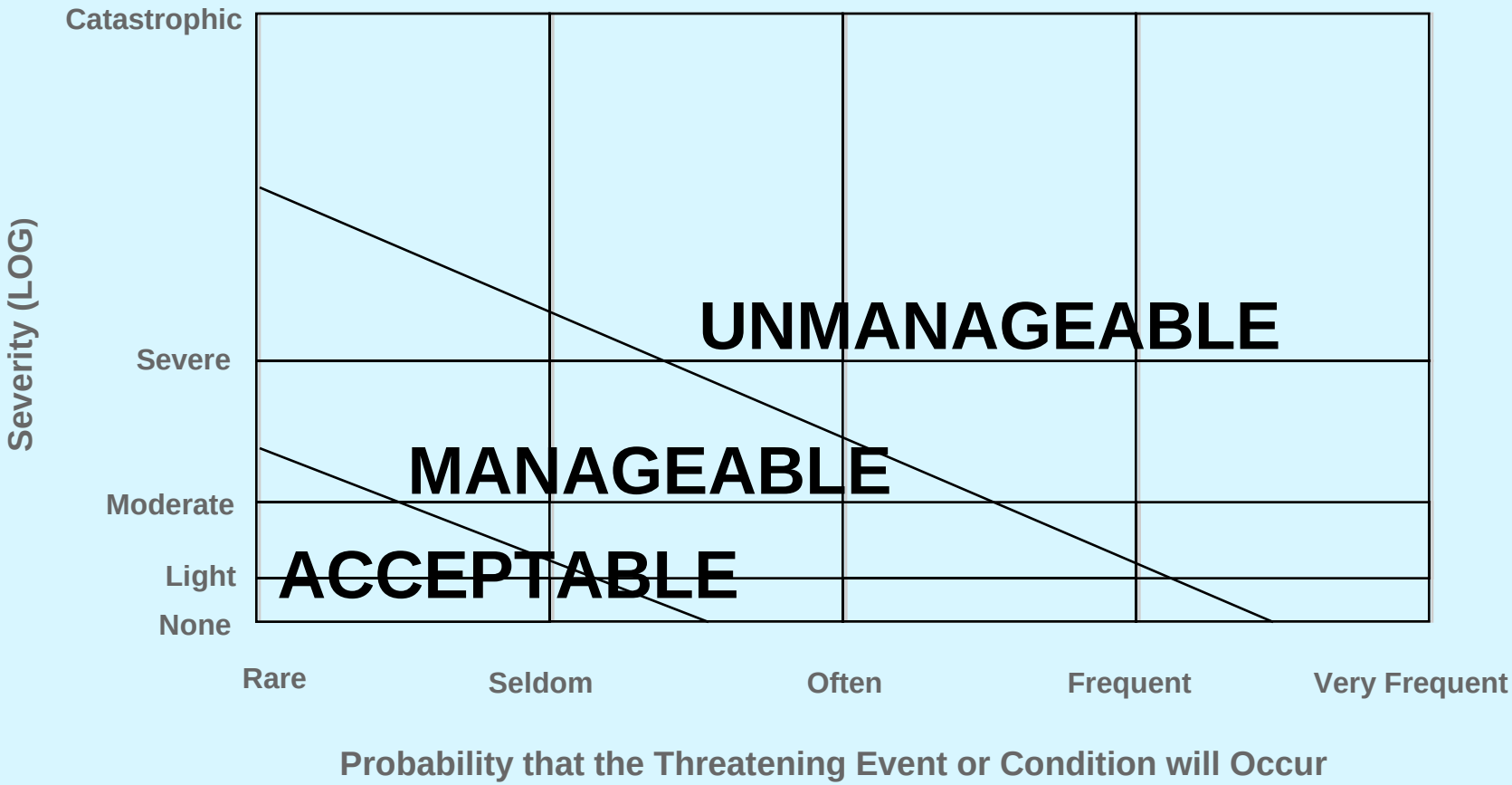
Investment Decisions Affect the Risk Profile



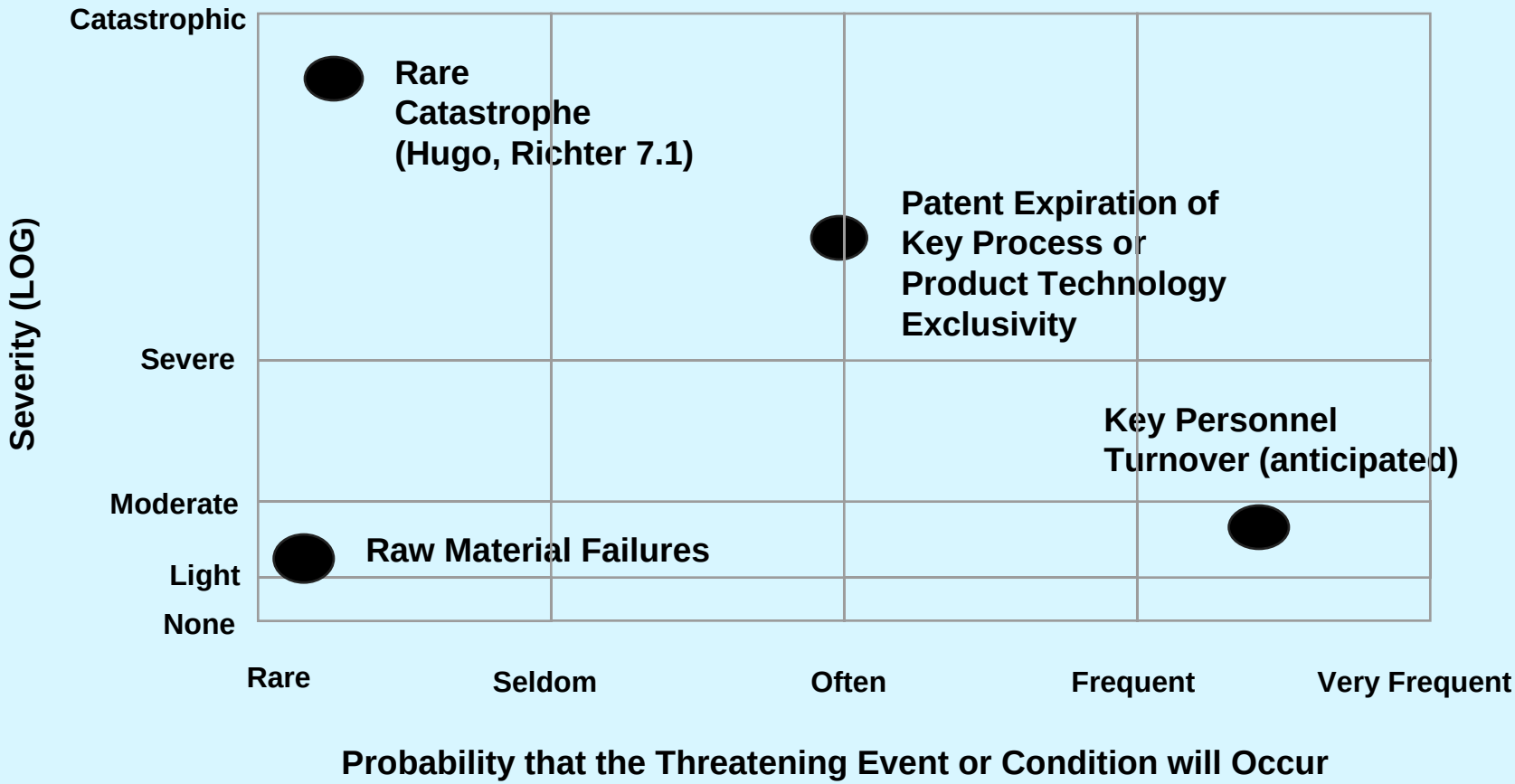
The Risk/Cost Relationship Defines Catastrophic Loss



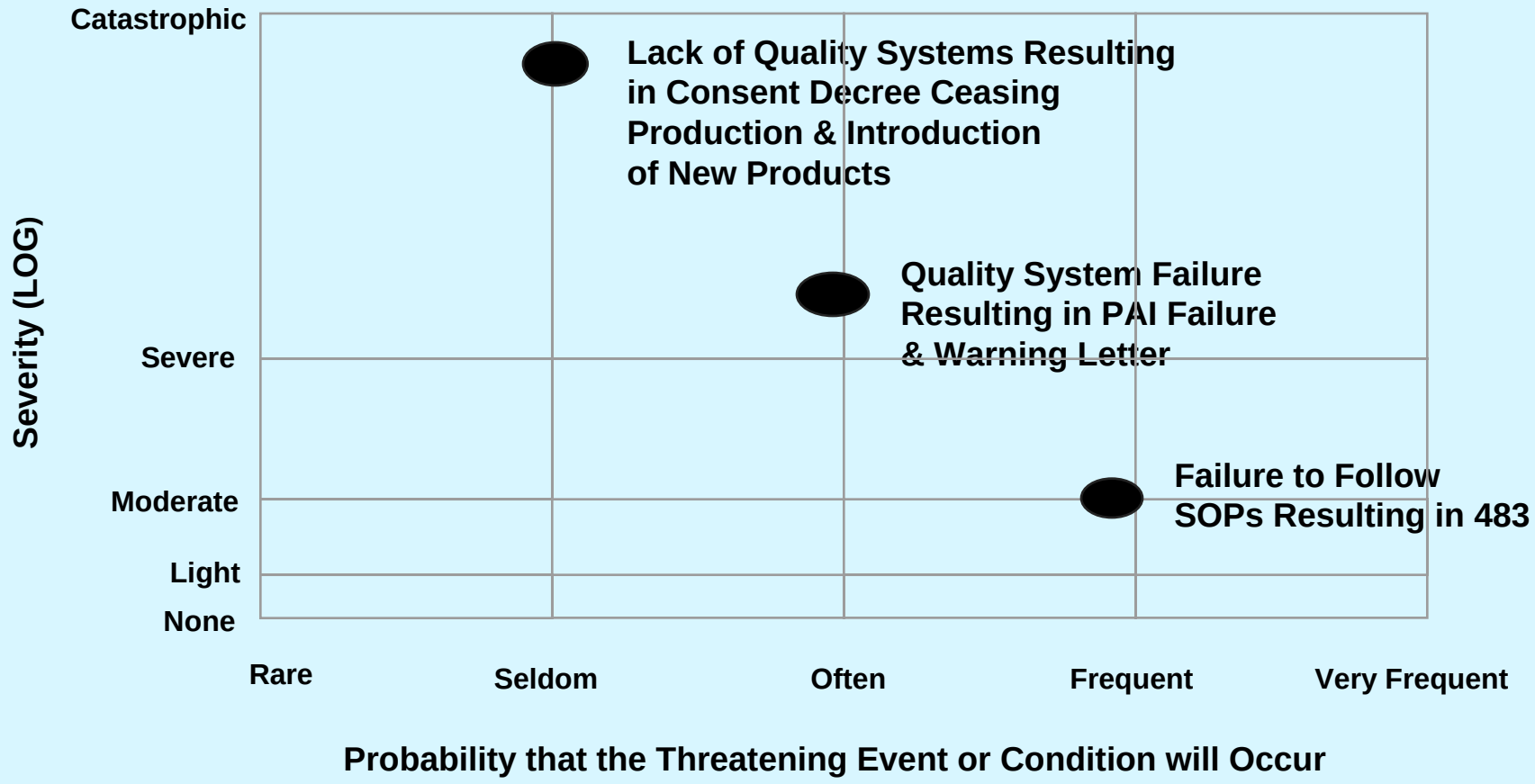
Vulnerability Analysis
Threat Assessment



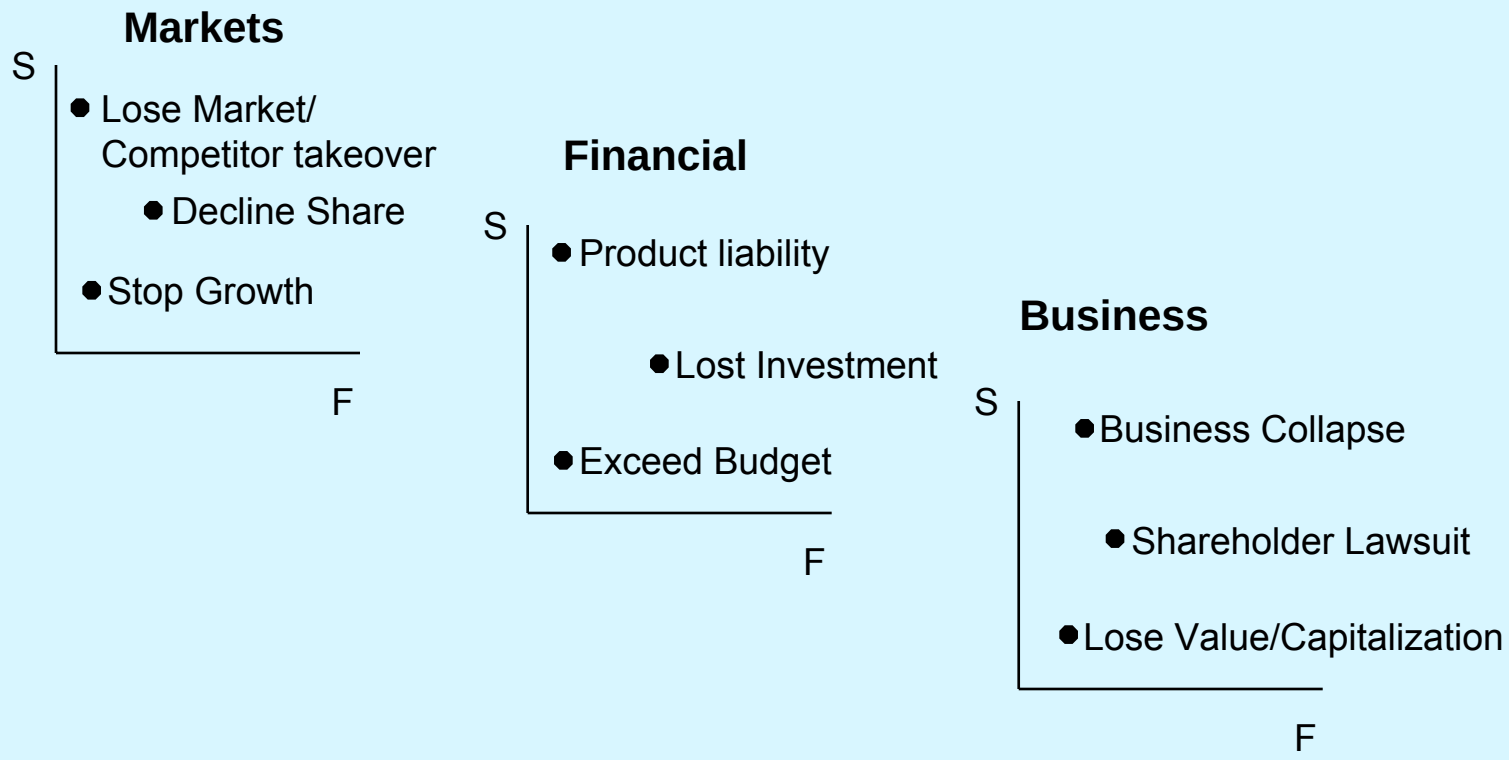
Example of Manufacturing Risk



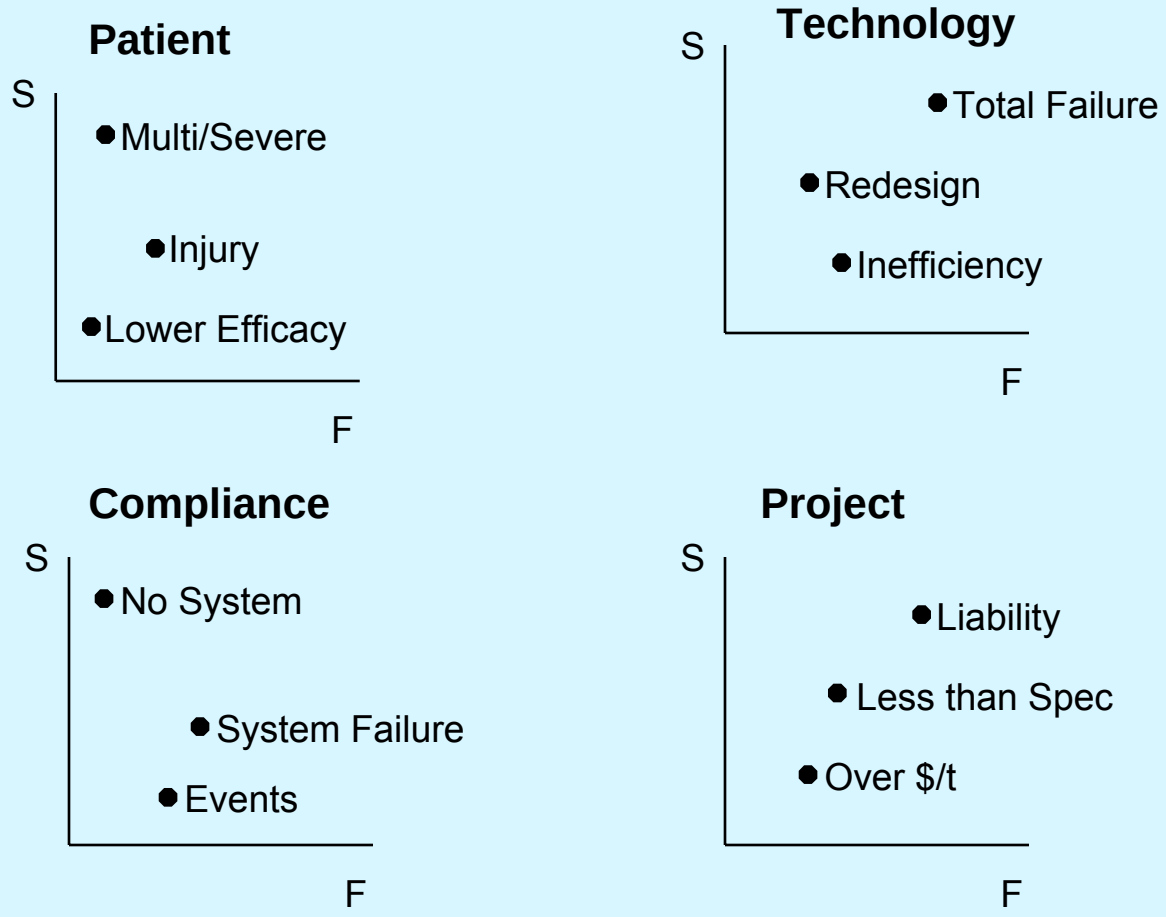
Example of Compliance Risk



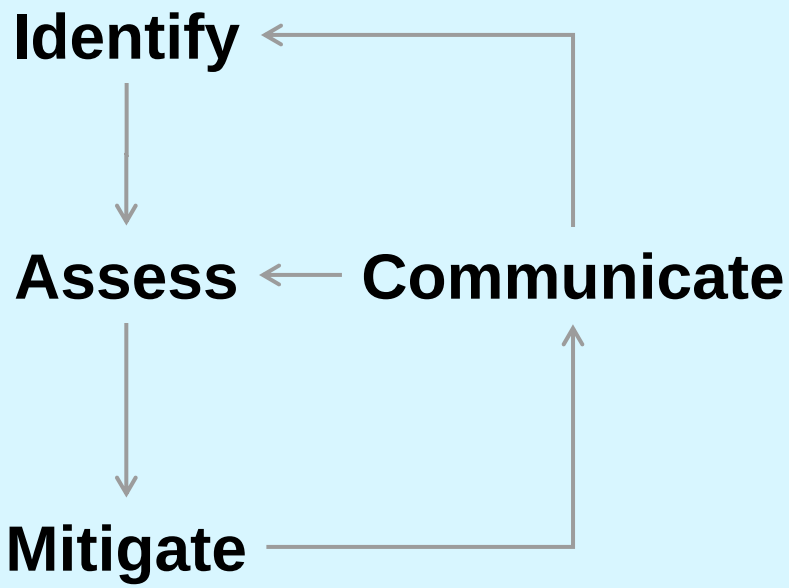
Evaluation for Multiple Risks



Evaluation for Multiple Risks, cont'd



Risk management process



Cases are for illustration purposes only and are derived from public information

Case A

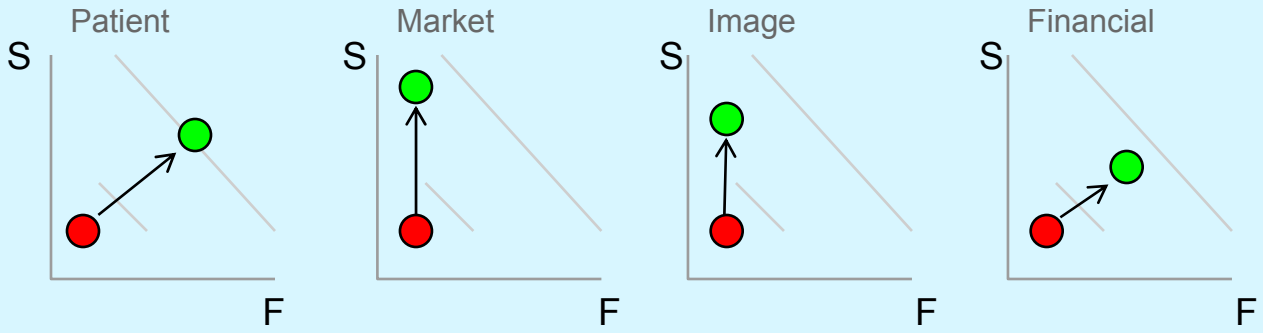
Steps / Risk	1. Development Phase 3	2. Regulatory Approval	3. Early Post-Marketing	4. Later Post-Marketing
Identify	Medical Panel Risk hypothesis	Medical officer comments → FDA Approves		New study for marketing phase 4 Study shows increased Heart incidents
Assess	Possibility of small level of incidents	Agree with company	No new data	Analysis concludes that results are inconclusive
Mitigate	Surveillance of side effects; post-marketing pharmacovigillance	Surveillance		1. Neutralize the study 2. Start new study
Communicate	Product has some risk	No special label restriction		Label restriction

Cases are for illustration purposes only and are derived from public information

Case A

The risk analysis after the study concluded that the risk was low given the hypothesis that the data and conclusion were incorrect.

The risk analysis of "If this is true . . . Then . . ." (Whole Systemic Analysis) could have evaluated the implications and consequences affecting patients → Market → Image → Financial



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Case A

Consideration could have been given to:

- **History of similar products**
- **First in class products**
- **Other product liability cases**
- **Magnitude of the financial consequences**

A cross-functional analysis by Medical, Marketing, PR, Financial:

- **Could have elevated the total risk from its severity given the potential of high frequency of incidents instead of mitigating and as an evaluation of loss of opportunities**

Cases are for illustration purposes only and are derived from public information

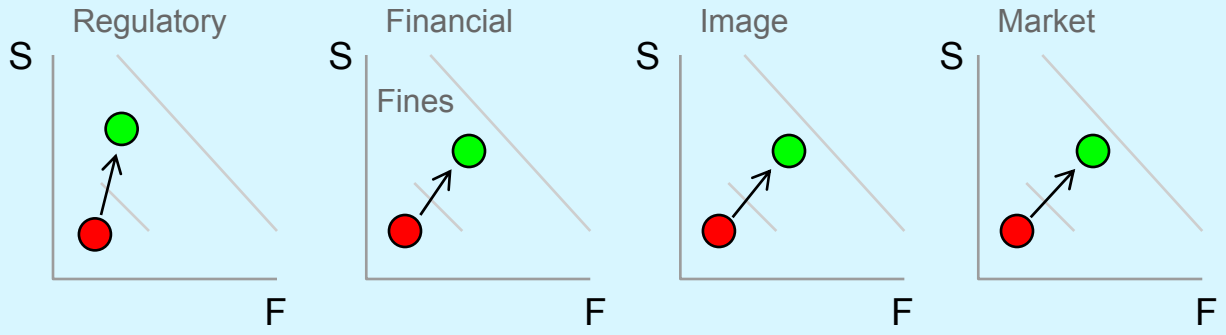
Case B

Steps / Risk	1	2	3	4
Identify	No Side Effects		Used for other indications	Major Growth and possible passive promotion
Assess			Sales Increase	No prohibition of usage or promotion No management system or controls
Mitigate				Insufficient
Communicate				

Cases are for illustration purposes only and are derived from public information

Case B

- **In this case there was no direct patient injury. The failure was in not identifying the regulatory non-compliance and the related consequences**
- **Regulatory action resulted in major fines and loss of credibility with agency**
- **The public was presented with a very negative image of the company and industry practices**
- **Conclusion Using a Risk FMEA Process could have identified the risk of non-regulatory compliance**



Prescription Drug User Fee Act

- Congress reauthorized the Prescription Drug User Fee ACT (PDUFA).
- In doing so, Congress stated FDA should have new commitments to improve the regulatory process, including strengthening and improving the review and monitoring of drug safety.
- FDA PDUFA goals included developing final guidances addressing good assessment, risk management, and Pharmacovigilance practices.

FDA Safety Guidances

FDA finalized three Industry Guidances in March 2005

- **Premarketing Risk Assessment**
- **Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment**
- **Development and Use of Risk Minimization Action Plans**

Risk Assessment

The Premarketing Guidance and Pharmacovigilance Guidance are designed to address Risk Assessment with a focus on Safety

- **Premarketing Assessments**
  - **During Clinical Trials**
- **Pharmacovigilance**
  - **During Post-Marketing**

Risk Minimization

The Development and Use of Risk Minimization Action Plans (RiskMAPs)

- **Post-Marketing minimization of a product's risks (safety) while preserving the benefits**
  - **Strategic safety program designed to meet specific goals and objectives in minimizing known risks**

Risk Assessment vs. Risk Minimization

Guidances state that Risk Assessment and Risk Minimization equal Risk Management

- **Risk Management is an iterative "dynamic" process of**
  - **Assessing a product's benefit-risk balance**
  - **Developing and implementing tools to minimize risks while maximizing benefits**
  - **Evaluating the effectiveness of those tools**
  - **Making adjustments to the tools to enhance the benefit-risk balance**

Guidances Emphasize Safety Profile

Guidances stress evaluating the risk profile of a product over its life-cycle (the "whole" of the product)

Largely focused on:

- **Understanding and establishing a safety profile**
- **Controlling and managing safety information**
- **Educating patients and providers, and**
- **Managing safety events**

Premarketing Guidance

By better understanding the risks during clinical studies

- **Be predictive in designing clinical studies**
  - **Based on pre-clinical work**
  - **Effects of related drugs**
  - **Nature and condition of target population**
  - **Nature of target disease**
  - **Nature and length of dosing (short term vs. long term)**

Pharmacovigilance Guidance

Better understanding risks during post-approval

- **Marketing usually increases significantly the number of patients exposed**
- **Observational Data in the "real world"**
  - **Scientific and data gathering activities related to detection, assessment and understanding of adverse events during marketing**
- **Identify and evaluate safety signals**
  - **Spontaneous reports**
  - **Data mining**

RiskMAP Guidance

Minimize risks during post-approval

- **Recognition that approval does not mean product is without risk**
- **In general, routine spontaneous reporting is sufficient**
- **Requires an understanding of the Risk vs. Benefit to the target population throughout the product's lifecycle, including off-label use**
- **Strategic safety program designed to meet specific goals and objectives in minimizing known risks**

Effective Risk Management

Managing and Minimizing Risk is difficult given:

- **Identification**
  - **Mixed product signals and information**
- **Assessment**
  - **Benefit-Risk Assessment**
  - **Different needs and interests**
  - **Various stakeholders**
- **Mitigation**
  - **Degree and Impact of Mitigation**
  - **Benefit-Risk of Mitigation**
- **Communication**
  - **Audience/Stakeholders**
  - **Effectiveness**

Questions?

Thank you,

Claudio

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Dan