U.S. Department of Health and Human Services
Food and Drug Administration

A Perspective on Risk Analysis for the GMP Initiative

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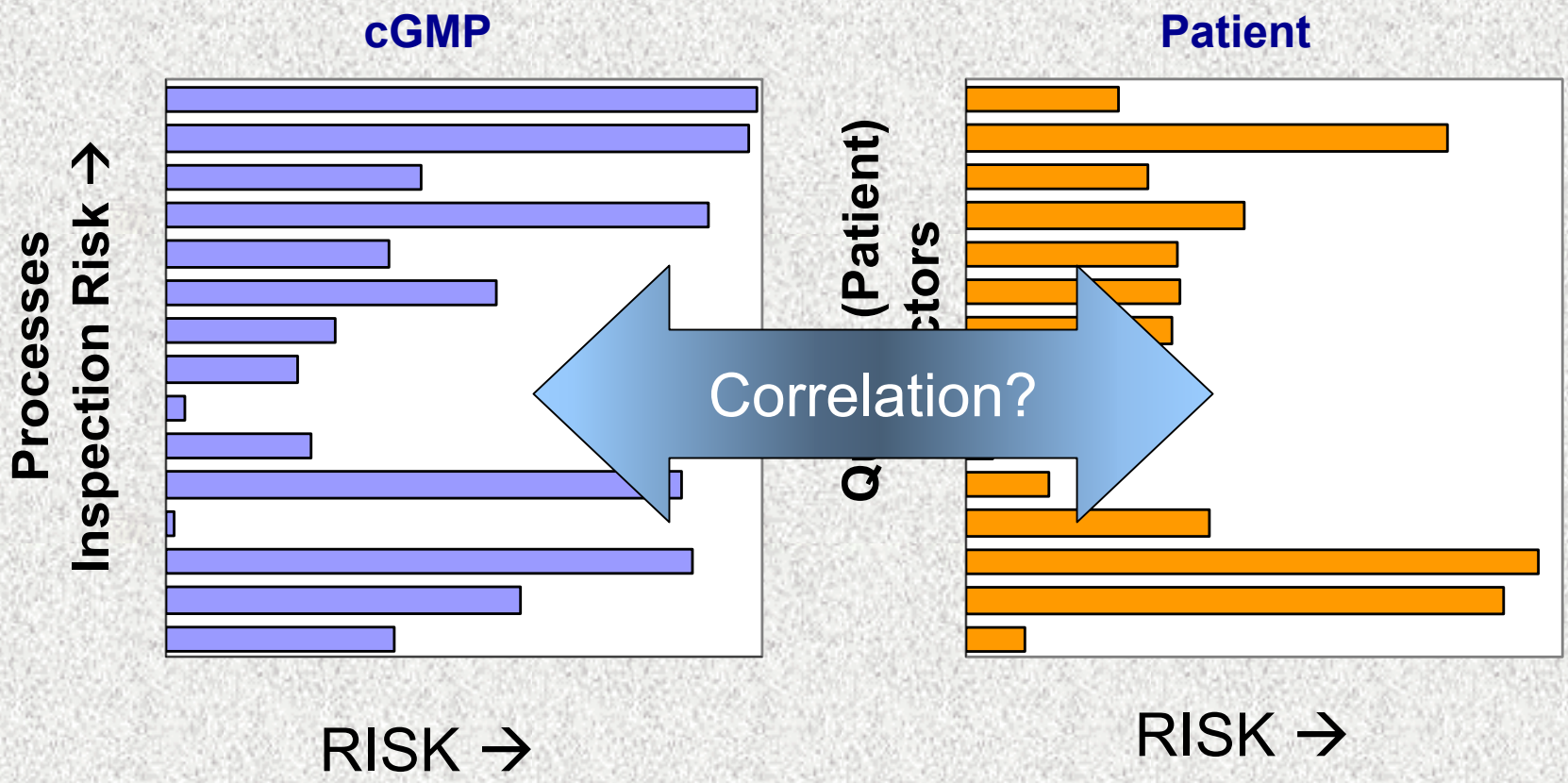
Outline

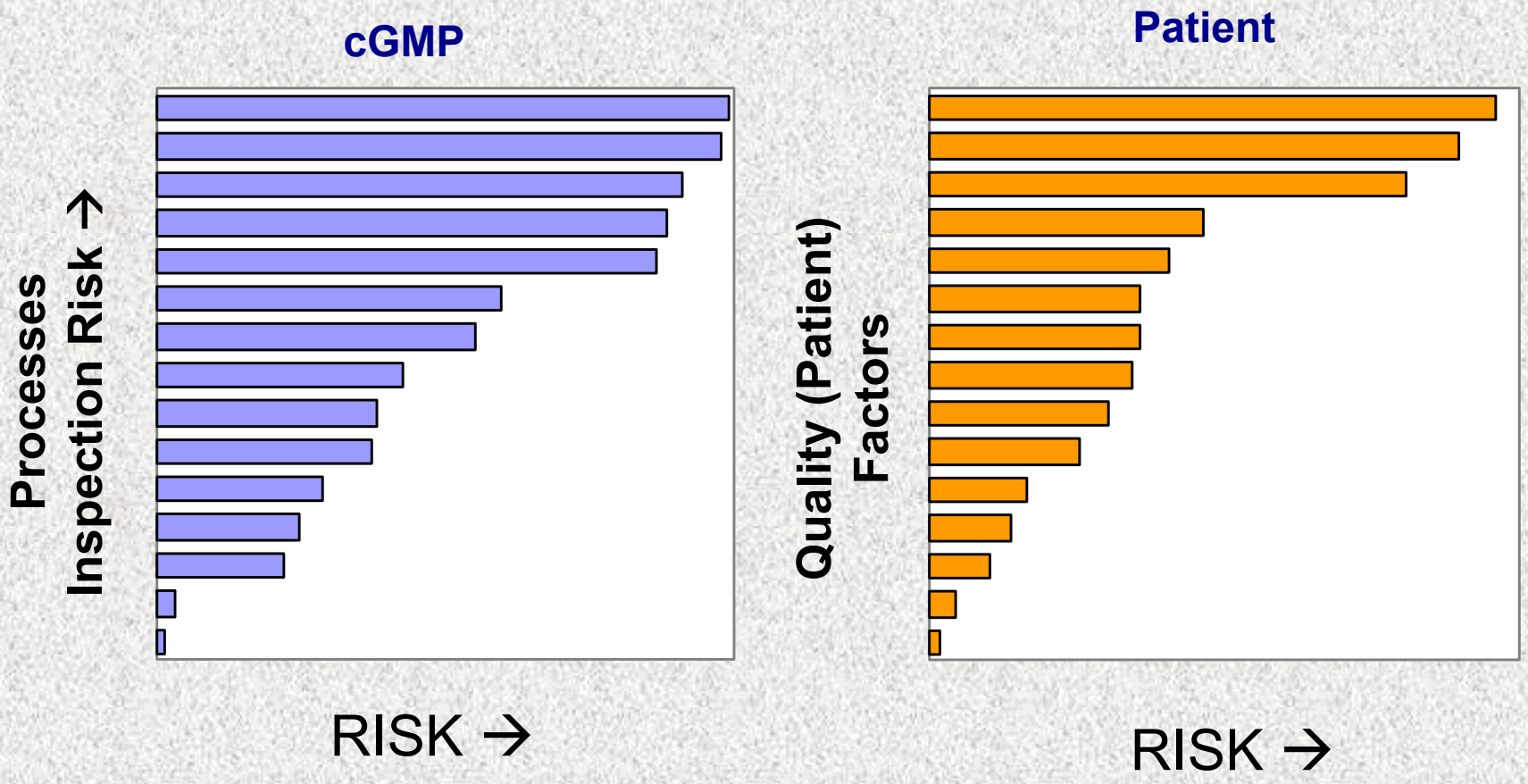
- The Premise and Questions
- Basics of Risk Analysis
- Possible Stages of Risk Assessments for GMP Initiative
- Risk Ranking Model for a GMP Initiative?
- Pilot Scale
- Conclusions

The opinions and ideas presented here are those of the author and do not represent policy or opinion of the FDA. This material is intended for discussion purposes only.

Premise: *Links Among Process (GMP) Risks and Patient Risks are Lost*



Goal: *Re-Link cGMP Risks with Actual Risks to the Patient*



The Question…

- Can Risk Management theory, tools, practice and philosophy be employed to re-link risks to the patient with the risks identified, perceived or otherwise implicated in the product quality regulatory process?

- How can we share a common language about risk, risk management and science-based decision making so that we can focus on developing a high-quality risk management model for product quality?

Getting Started…

- What theories, tools and lessons learned in risk analysis can help address these questions?
- Given the need for a significant shift in the approach to risk management, how do we begin the change process?
  - Are there off-the-shelf models and tools that might be used, i.e., at a pilot-scale?
  - What kinds of RM processes can be used to foster changes needed both the regulatory and industrial spheres?

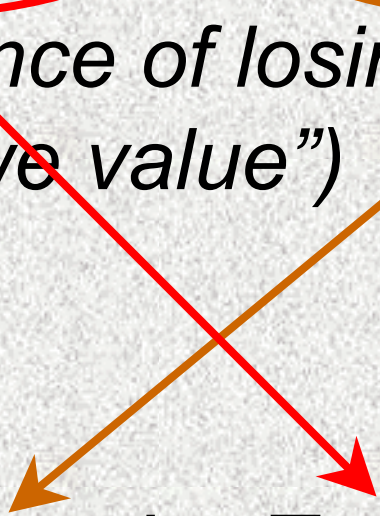
Basic Risk Analysis

Starting with the Some Basics

Risk is intuitive and familiar to everyone, yet few among us define risk carefully and formally enough for complex risk analysis.

Risk = "exposure to a chance of loss"

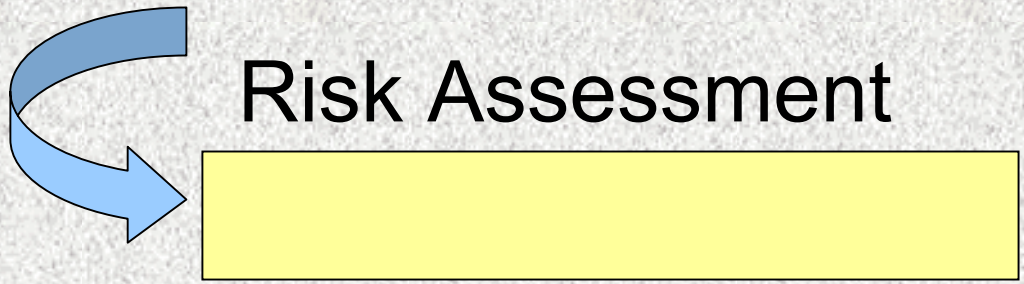
(or, Risk = "chance of losing something we value")



Risk = Hazard x Exposure

$Risk_{Consequence}$ = Hazard x Exposure

Contemporary Risk Analysis

- Includes four major activities:
  - Hazard Identification
  - Risk Assessment
  - 
  - Risk Communication

Risk Assessment Precedes Risk Management

- Risk assessment is not a single process, but "a systematic approach to organizing and analysing scientific knowledge and information." NRC (1994)

- Various paradigms exist for the *execution* of a risk assessment in public health; however, all paradigms have in common *fundamental principles*.

Risk Assessment Asks:

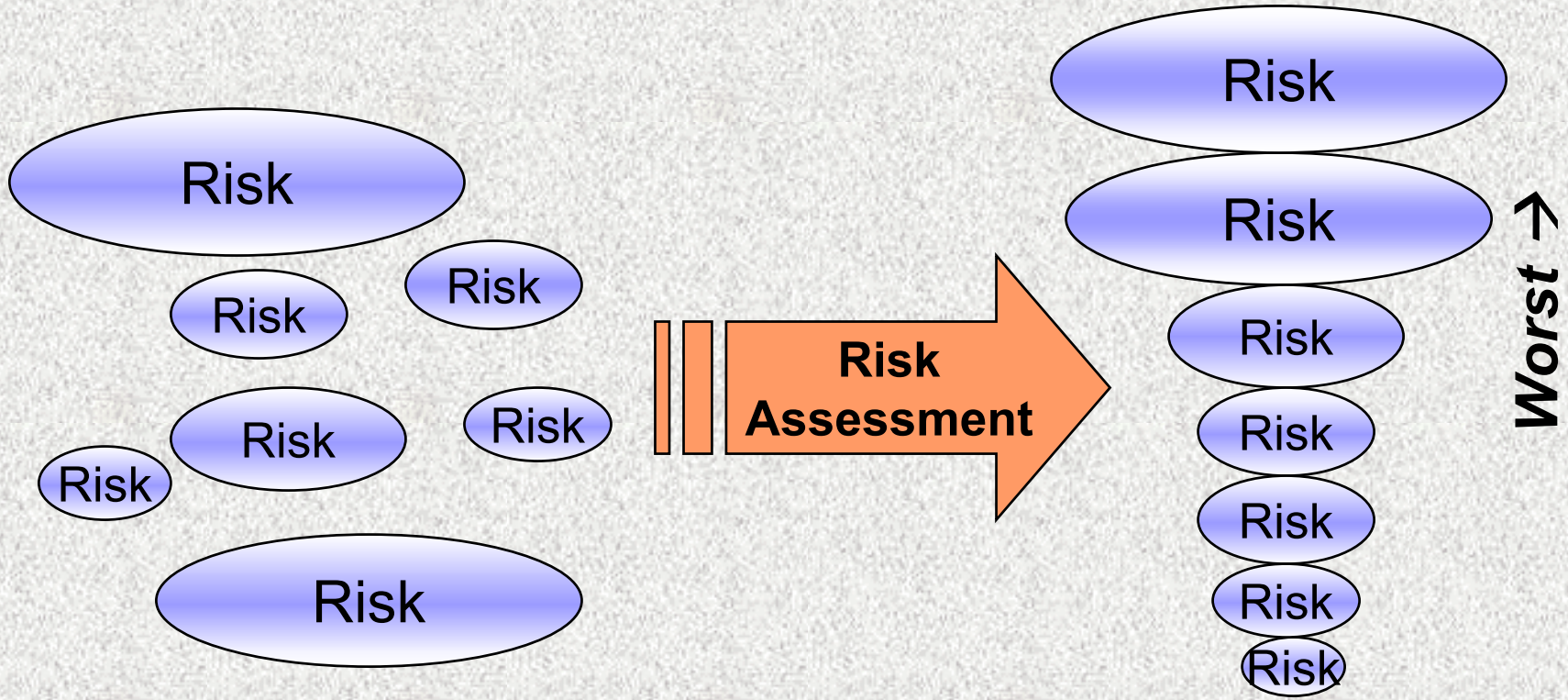
- What can go wrong?
- What is the likelihood it would go wrong?
- What are the consequences?

Risk Management Asks:

- What can be done?
- What options are available?
- What are risk trade-offs in terms of risks, benefits and costs?
- What are the impacts of current management decisions on future options?

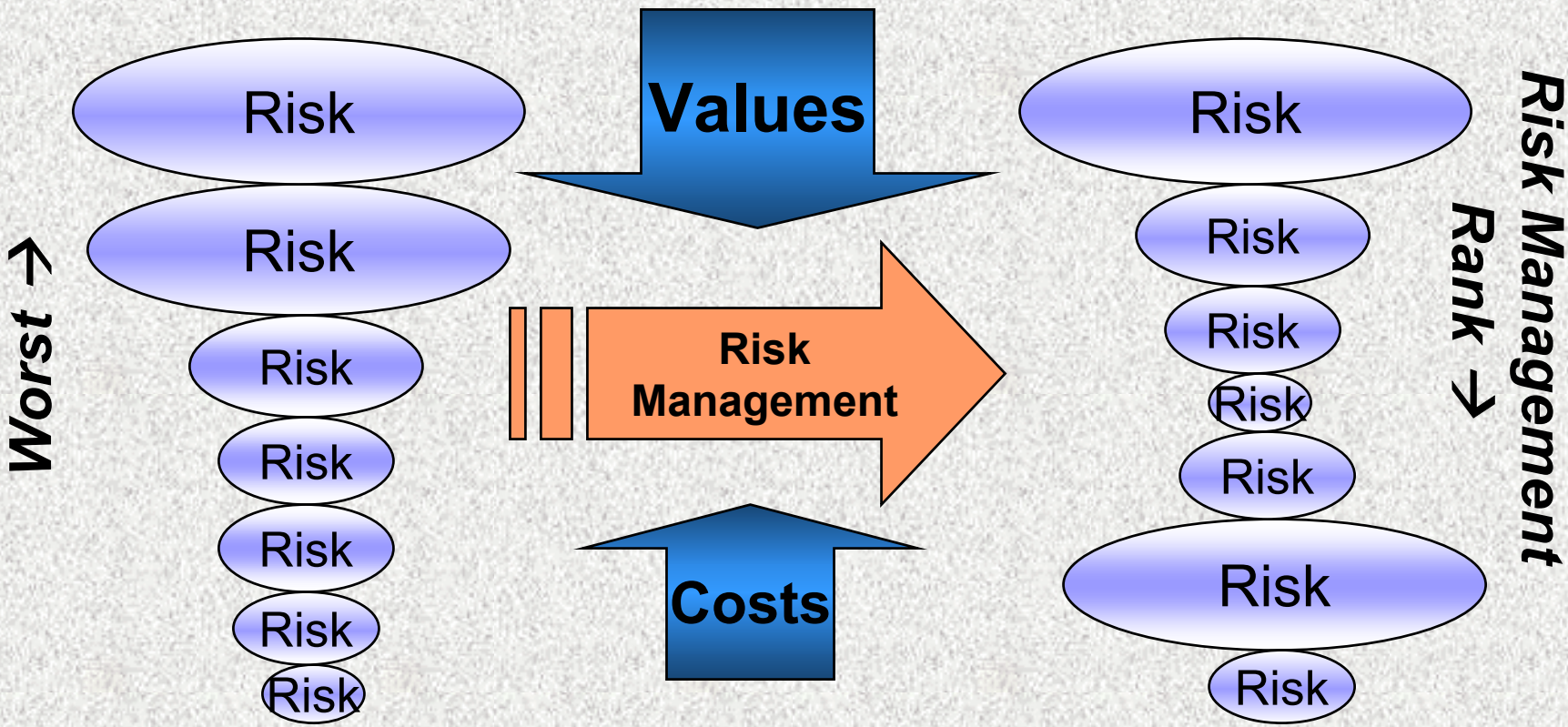
Risk Analysis in a Democracy

- Risk *assessments* provide the "facts" for risk analysis.

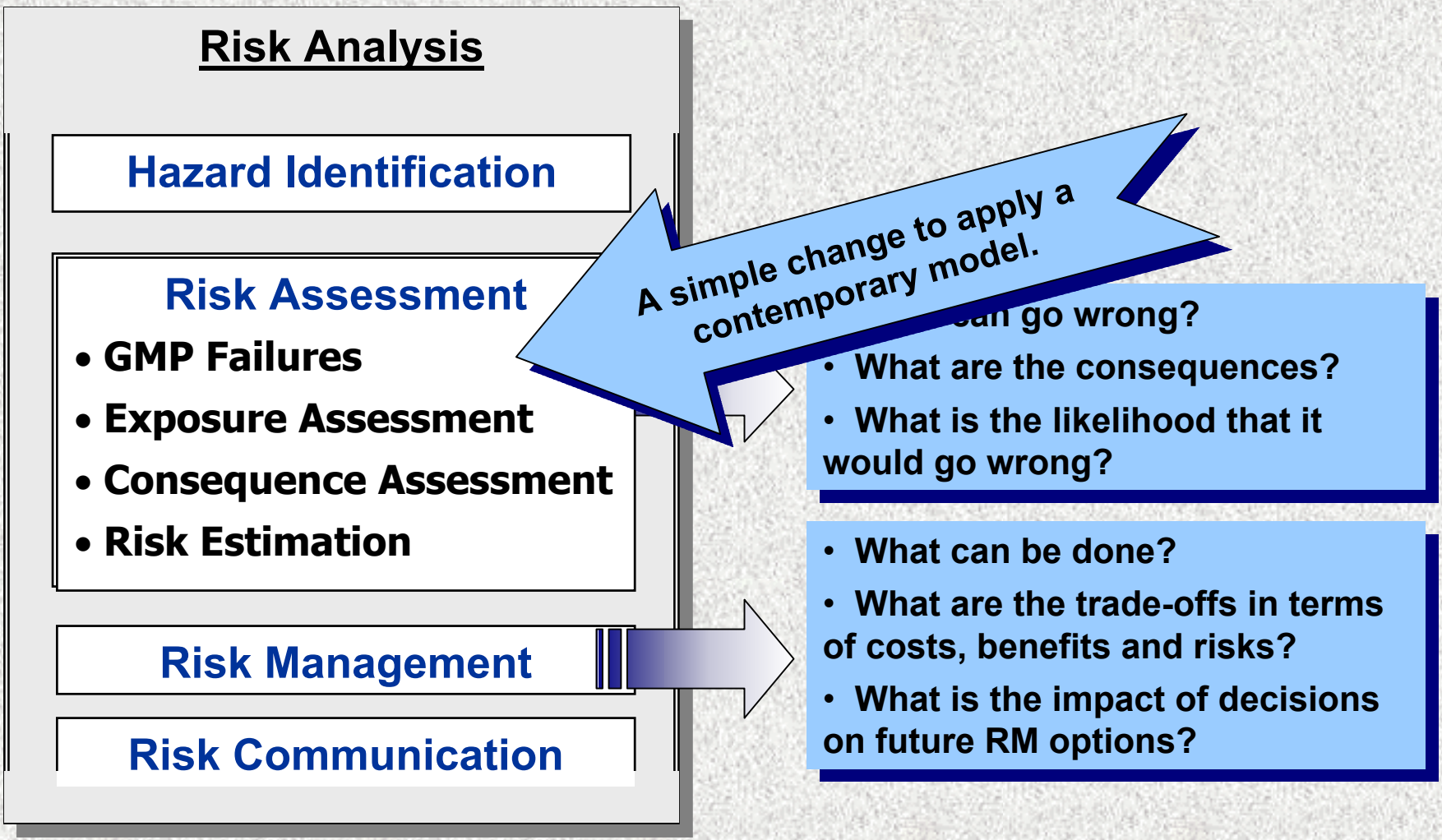


Risk Analysis in a Democracy

- The risk *management* decisions about which risks to manage are value-laden decisions.



Translating Risk Analytic Paradigms



Possible Stages of Risk Assessment for the GMP Initiative

Hazard Identification

- *What can go wrong?*
  - Identify hazards: *events*
  - Identify hazardous *agents* (chemical, biological, physical)
- *How severe are the potential consequences?*
  - Given the event occurs, is the consequence catastrophic? Mildly annoying?
- *How likely are the events to occur?*
  - Essentially a crude risk estimate for initial prioritization purposes.

Exposure Assessment

- Release Assessment: *How "much" of the hazardous event occurs?*
  - Example: Does a "non-sterile" event involve 1 or 10,000 vials?
- Pathway analysis: *If the hazardous event occurs, what pathways are there that expose humans to the hazard?*
- Extent of exposure: *If a hazardous event occurs, how many people are potentially exposed?*

GMP Failure (Release) Assessment

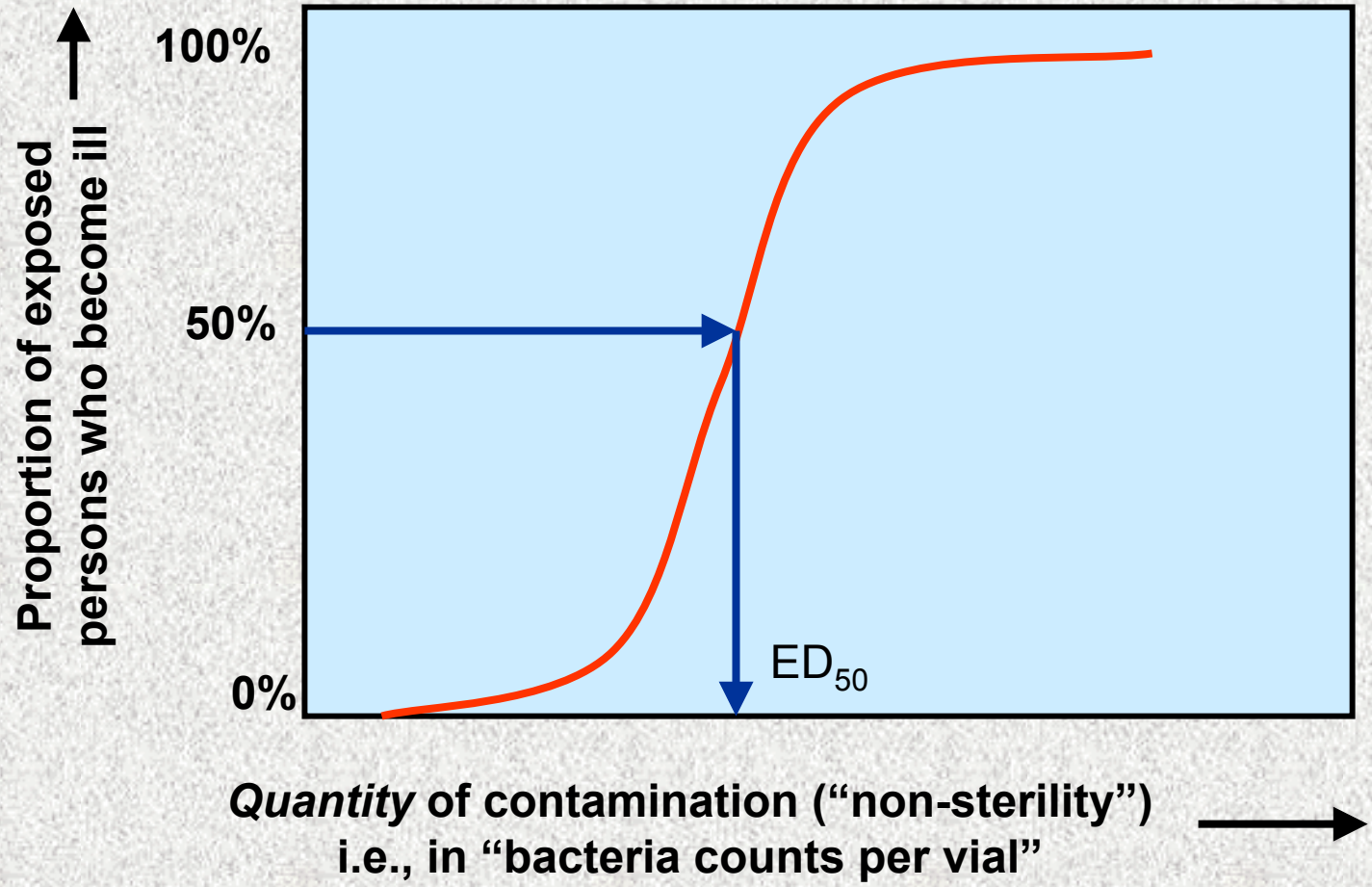
- How frequent are the identified GMP events (hazards)?
- Boundary of release? Process line, plant, warehouse, distributor?
- Release rates (“GMP Faults”) are obtained in fault tree assessments, empirically, historical data, expert analyses.
  - Example: FMEA

Consequence Assessment*

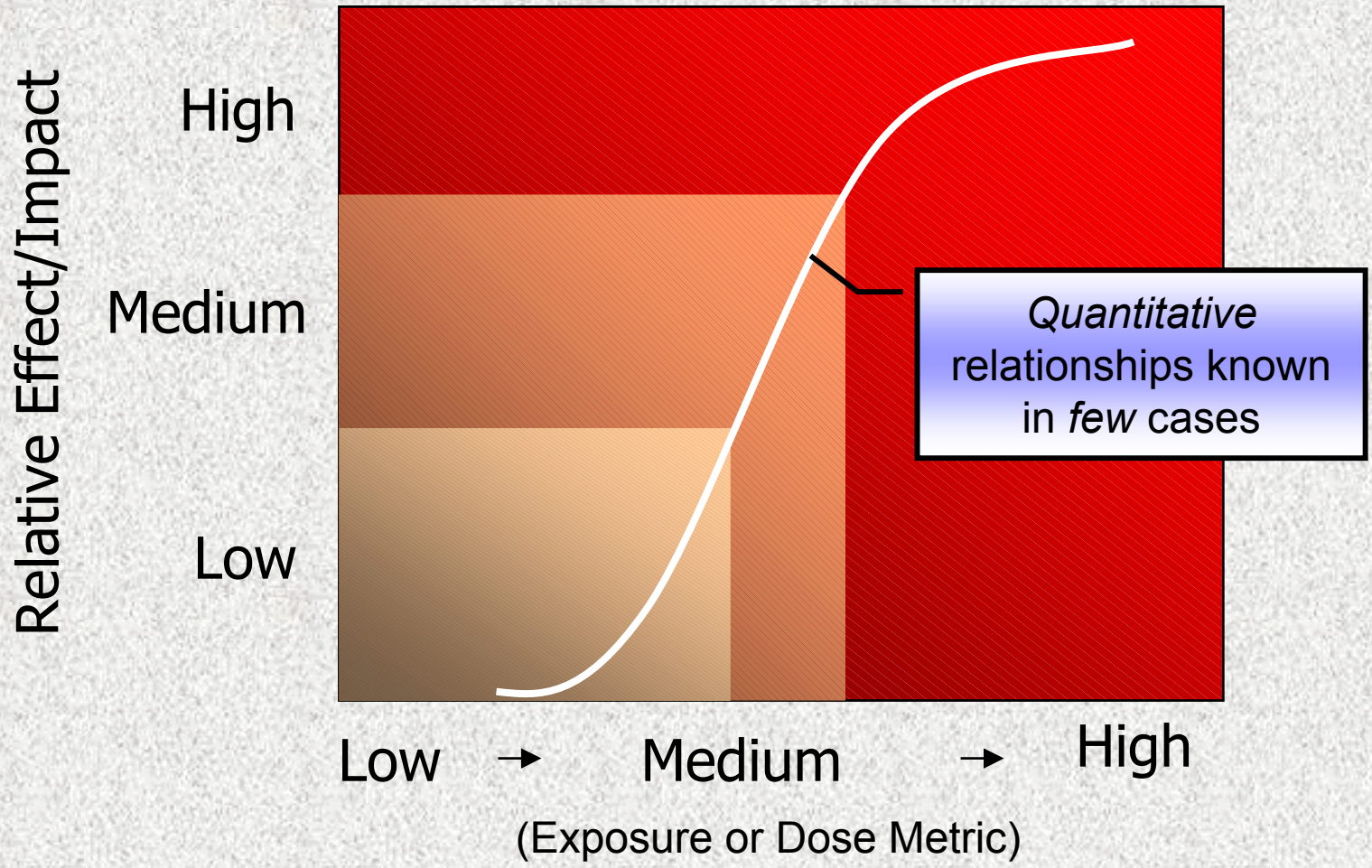
- *Given exposure to the hazardous event/agent, what is the likelihood of harm under a pre-defined endpoint?*
  - Endpoint examples:
    - Death
    - Illness
    - Worry
    - OAI

*A.K.A. “Dose-Response Assessment” (see next slide)

Consequence Assessment



Qualitative Consequence Assessment

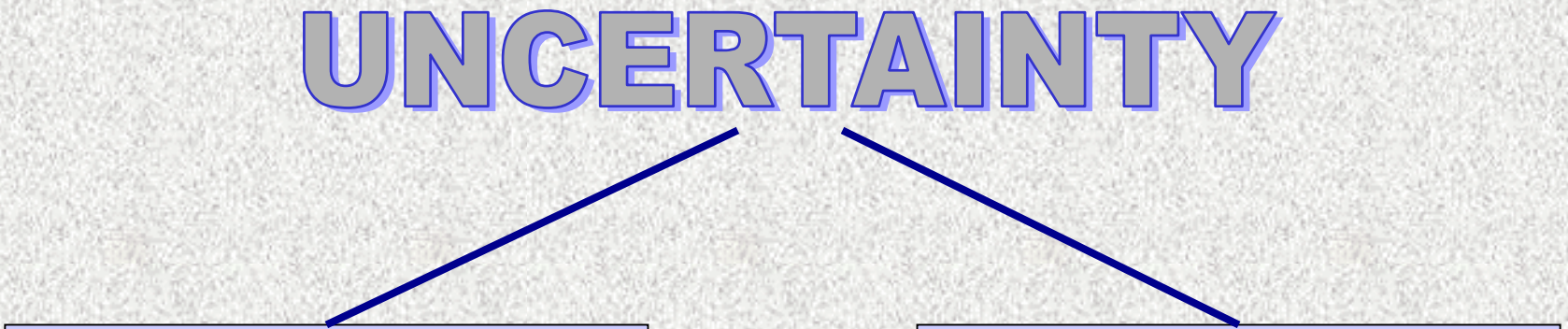


Risk Estimation

- Bring together the information about
  - the hazard,
  - the extent of exposure to the hazard,
  - the consequences of exposures, and then
  - *estimate the risk.*

- Includes a critical analysis of uncertainty in both the data and risk assessment models.

Uncertainties in Risk Assessment



- Data
- Parameters
- Model

- Temporal
- Spatial
- Inter-individual

Conceptual Models for RM in GMP Initiative

The cGMP Risk Management Problem

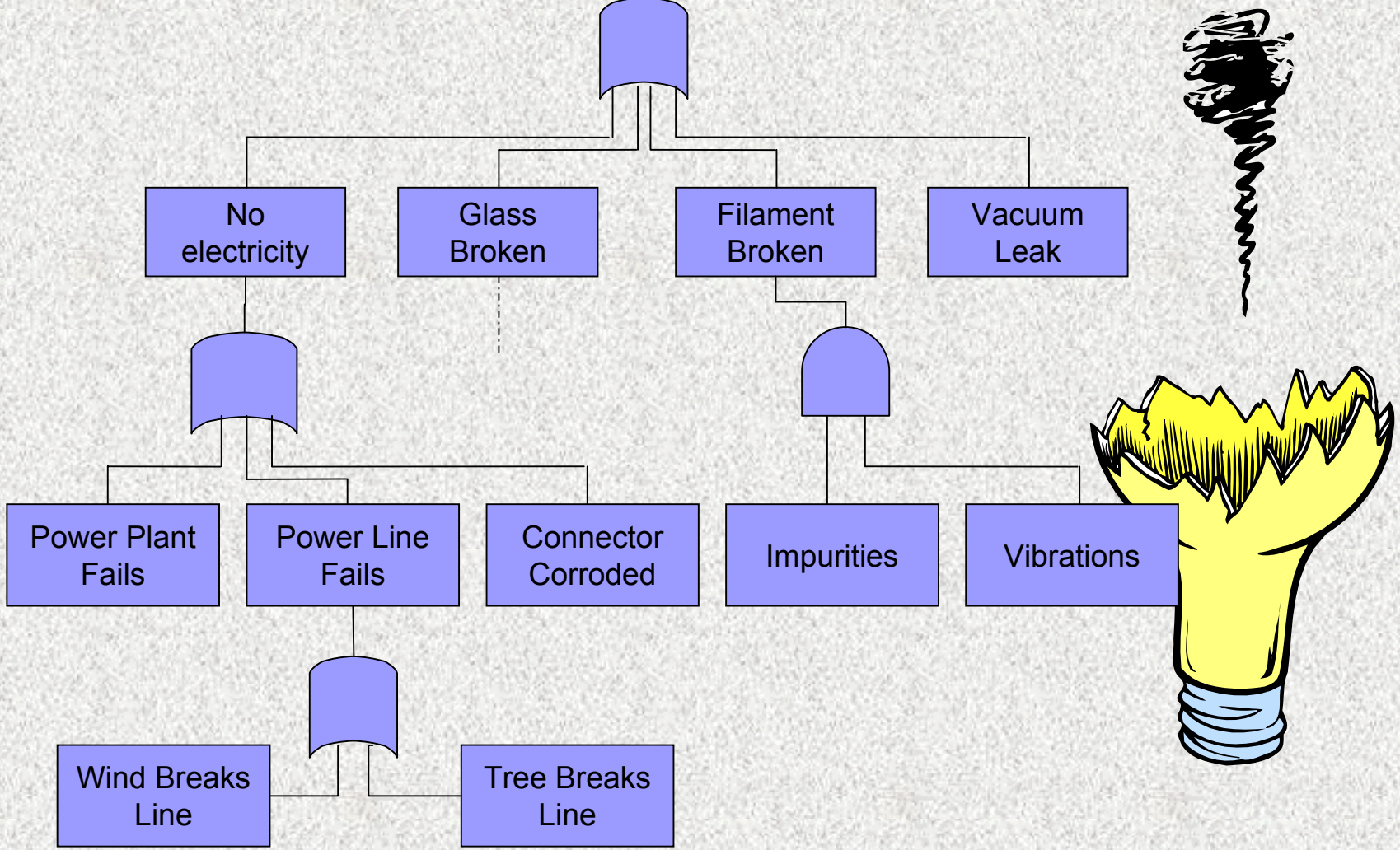
- *Diverse* GMP failure (hazards) are identified.
- Wide-ranging risk (= chance that exposure to the e]).

  How can we objectively rank "apples and oranges" among the "potatoes and beans?"

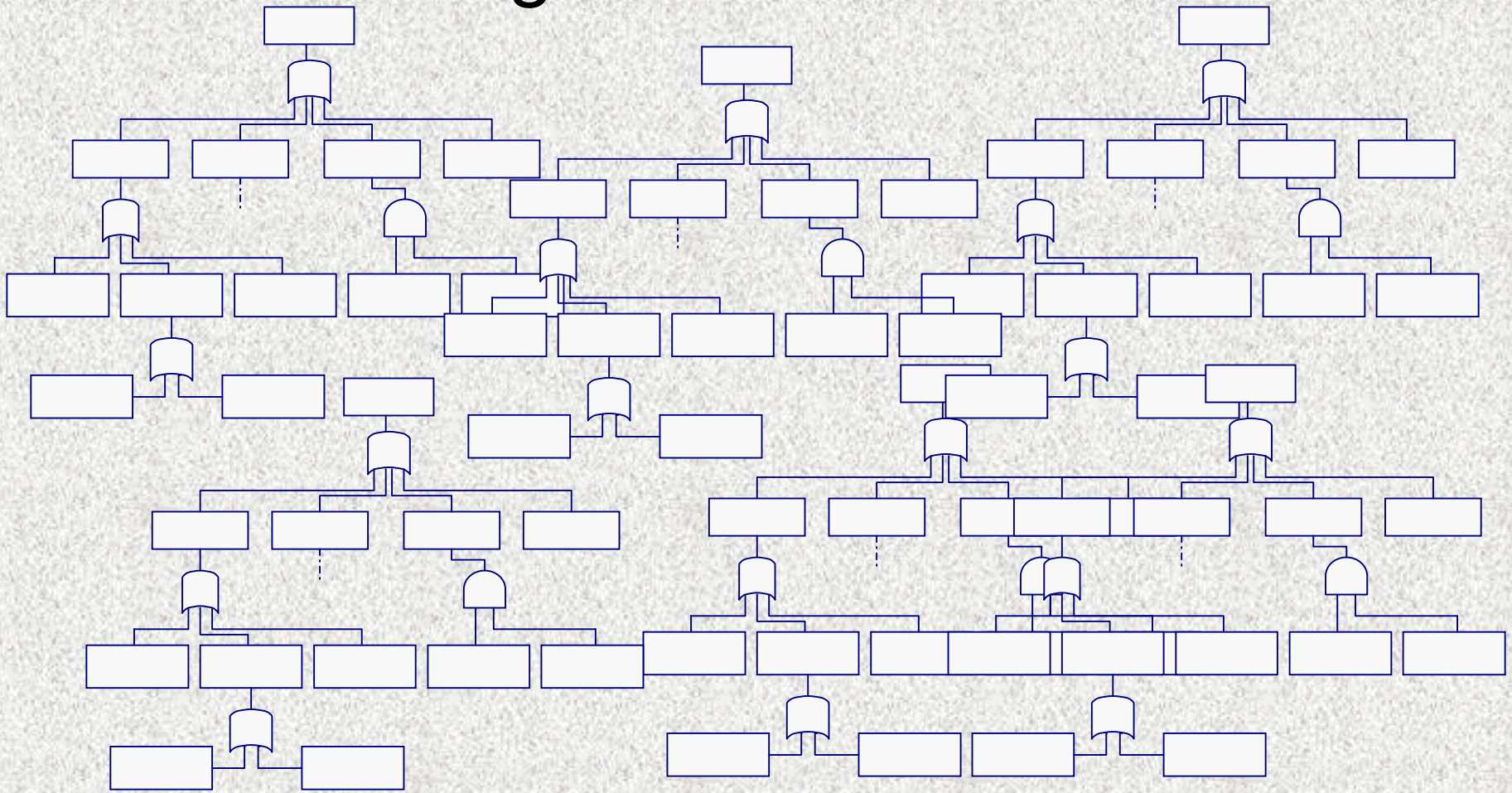
  y).

  too vast an undertaking.
- Ranking of risks for re-linking worst GMP risks with worst health risks, etc.

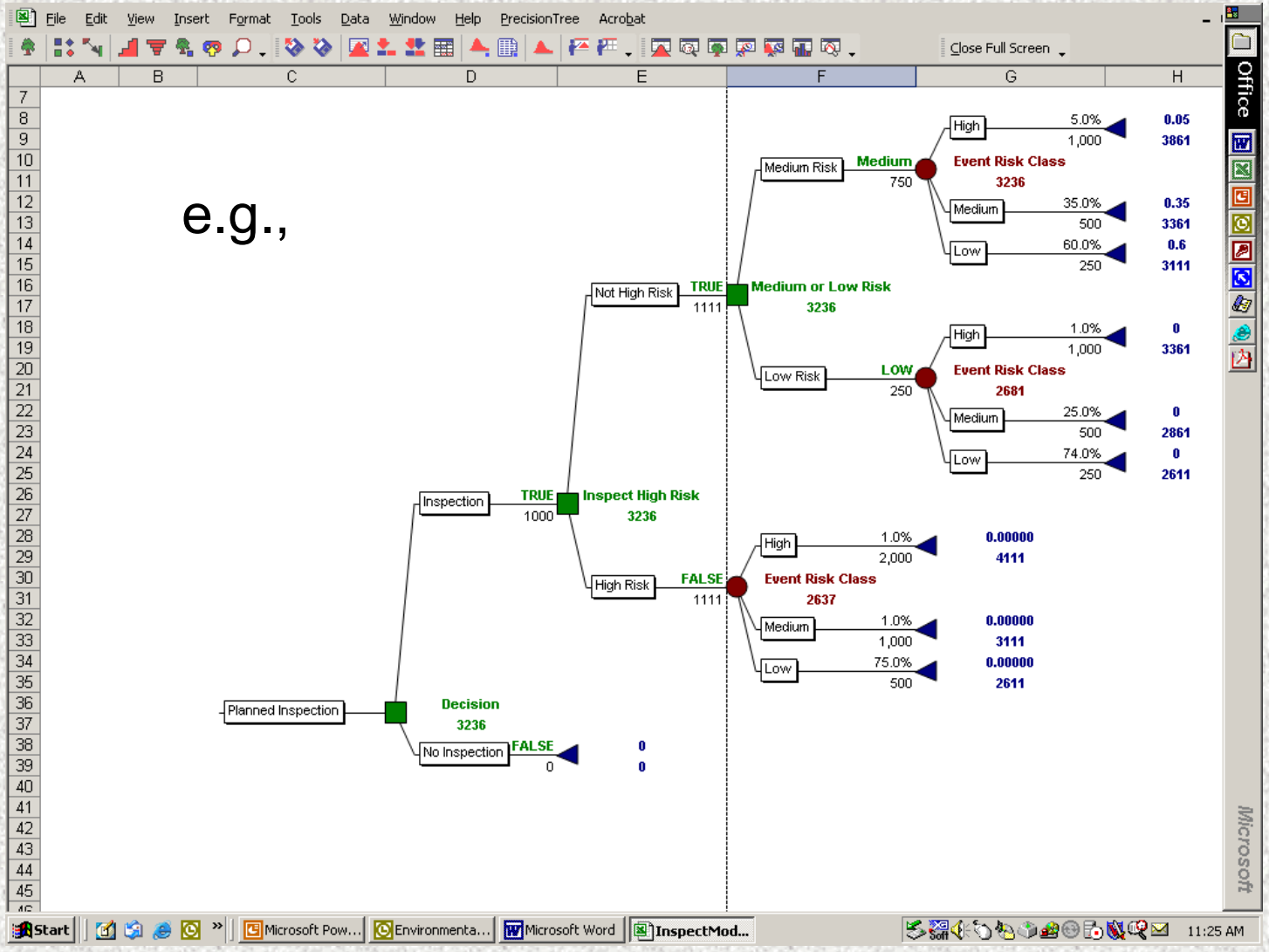
Fault Trees for Bulb Fails each process?



Faults Magnified *N*-fold for a Simple Manufacturing Process



Decision Analyses for Each Hazard Multiplies Complexity!



Solution? A Multifactor Approach to GMP Risk Management

- Multifactor methods already exist.
- Some tools (software) already developed.
- Appropriately-scaled approach to
  - the question,
  - the data quality,
  - the nature of the decision, and
  - the understanding of the overall process.

State the Assumptions

- E.g., assume that health risks were linked to GMP “compliance risks” previously, i.e., the historical basis of regulation.

  Historically based assumption:

  ↑compliance → { **↓Health risk**; **↑quality** }

- Given the assumption, can GMP “compliance risk” be modeled as a surrogate of health risk?

Identify the GMP Failures (Hazards)

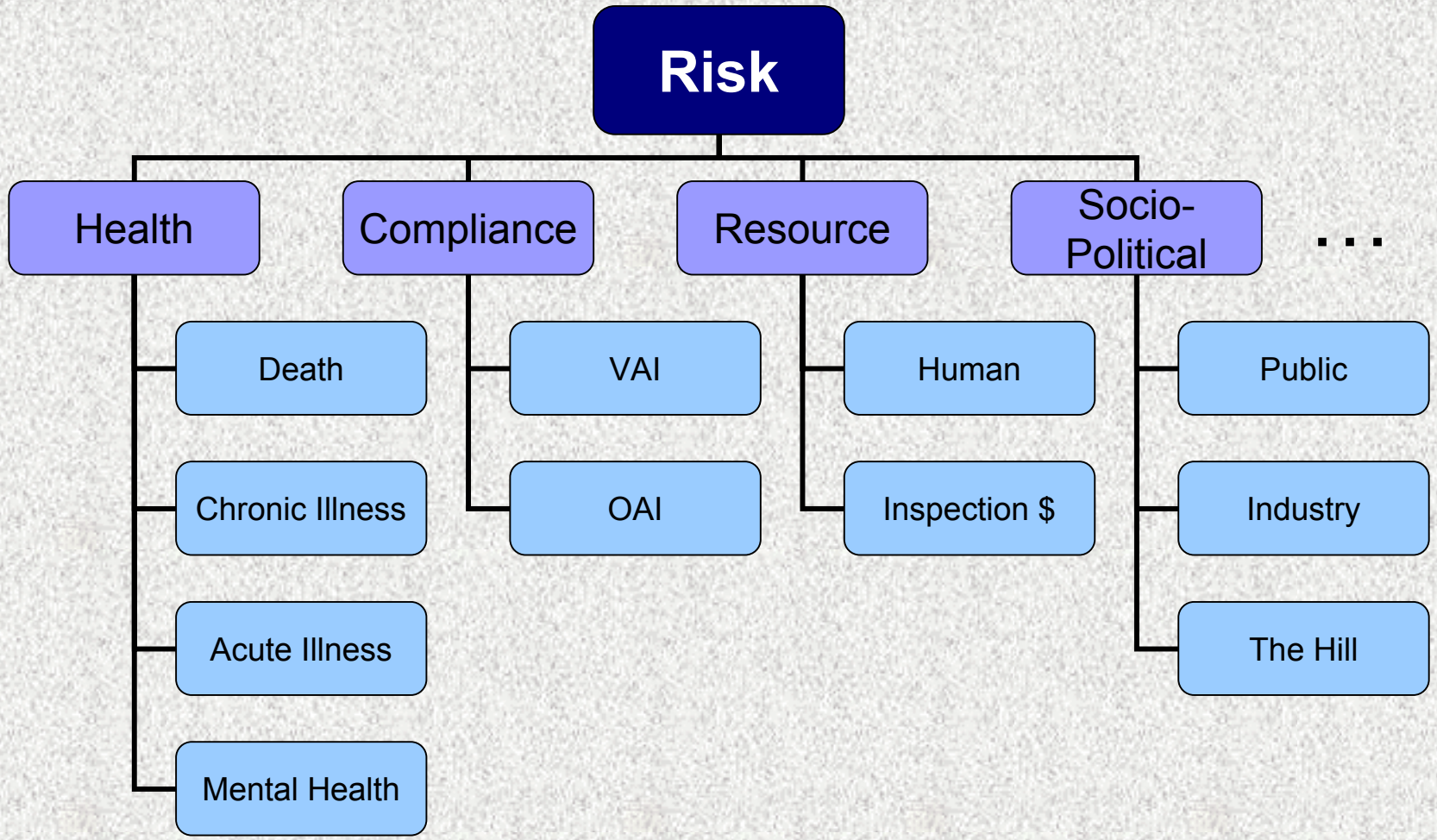
- What can go wrong?
- Top level organization of hazards:
  - Health | Compliance | Resources | Sociopolitical
- Second level (detail) organization:
  - Sterility (microbial contamination)
  - Dose (formulation)
  - Toxicity (chemical contamination)
  - Physical hazards (physical contamination/defect)
- Fine detail: “risk factor” event descriptors.

Sort the Hazards/Risks by Major Categories

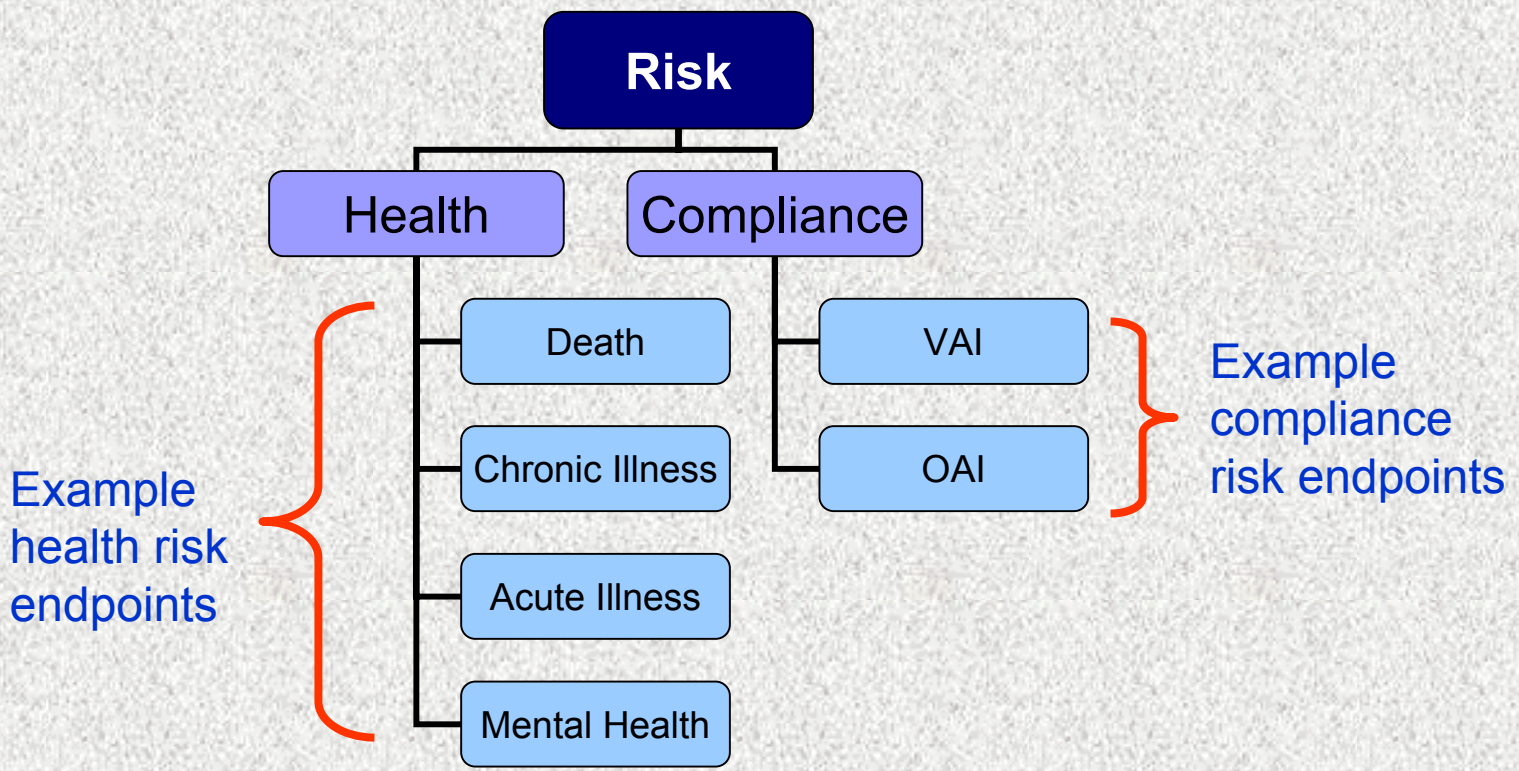
- Start with assumptions.
- State questions to be answered.
- Sort under the questions.
- Re-sort if new patterns emerge.

For example, (next slide)…

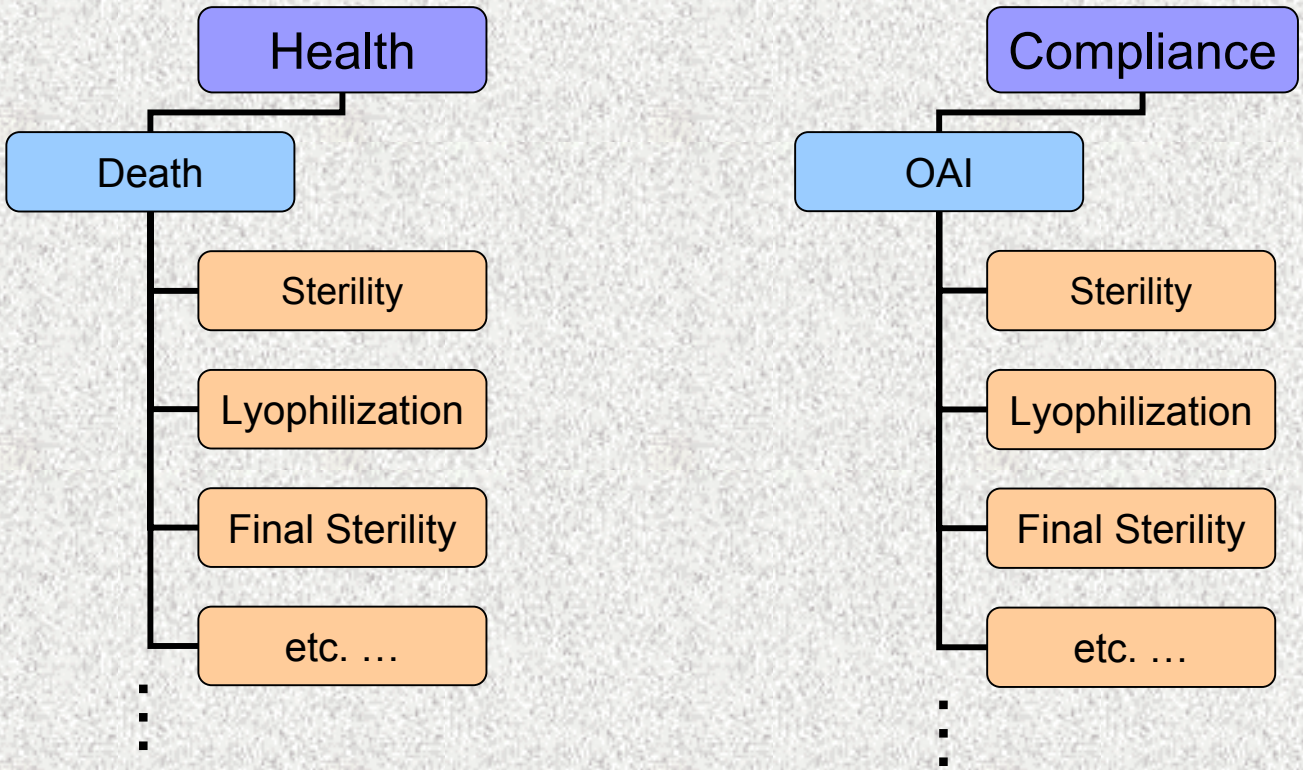
Organizing a Multi-factorial Risk Model



Focused Multi-factorial Risk Model



Risk factors for a given endpoint…



Estimate the Prevalence

- The prevalence of inspection findings for a given type of event are initial estimates of probabilities necessary for risk management modeling.
- Failure analysis “in plant.”
- Failure in compliance inspections.
- Human adverse events.

For each hazard…

Health Endpoint	Probability of Occurrence				
	Very Low	Low	Medium	High	Very High
Death	*Medium*	*Medium*	*High*	*High*	*High*
Chronic Illness	*Low*	*Medium*	*Medium*	*High*	*High*
Acute Illness	*Low*	*Low*	*Medium*	*Medium*	*High*
Worry	*Low*	*Low*	*Low*	*Medium*	*Medium*

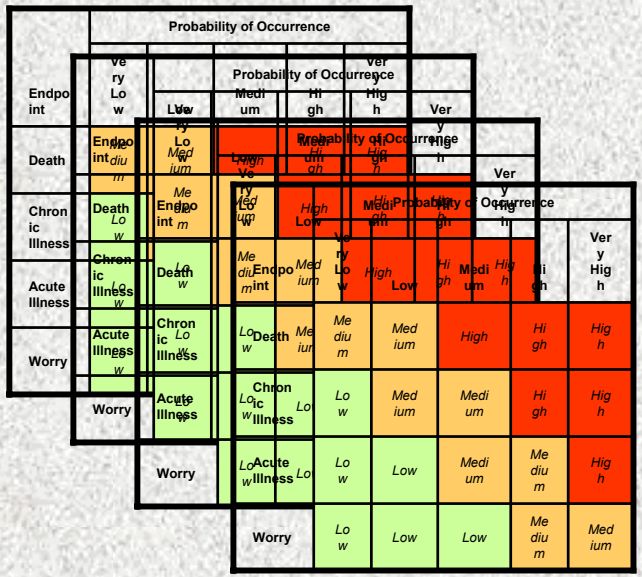
The modeler's view… (for example)

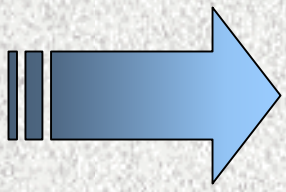
Health Endpoint	Probability of Occurrence				
	Very Low	Low	Medium	High	Very High
Death	5	4	3	2	1
Chronic Illness	6	5	4	3	2
Acute Illness	7	6	5	4	3
Worry	8	7	6	5	4

For each hazard…

Compliance Endpoint	Prior History of Actions				
	Never Violations	Few Viol.	Average Viol.	Some Viol.	Many Viol.
OAI	*Medium*	*Medium*	*High*	*High*	*High*
VAI	*Low*	*Low*	*Medium*	*High*	*High*
Other?	*Low*	*Low*	*Low*	*Medium*	*High*

Scoring, then prioritize multiple hazards

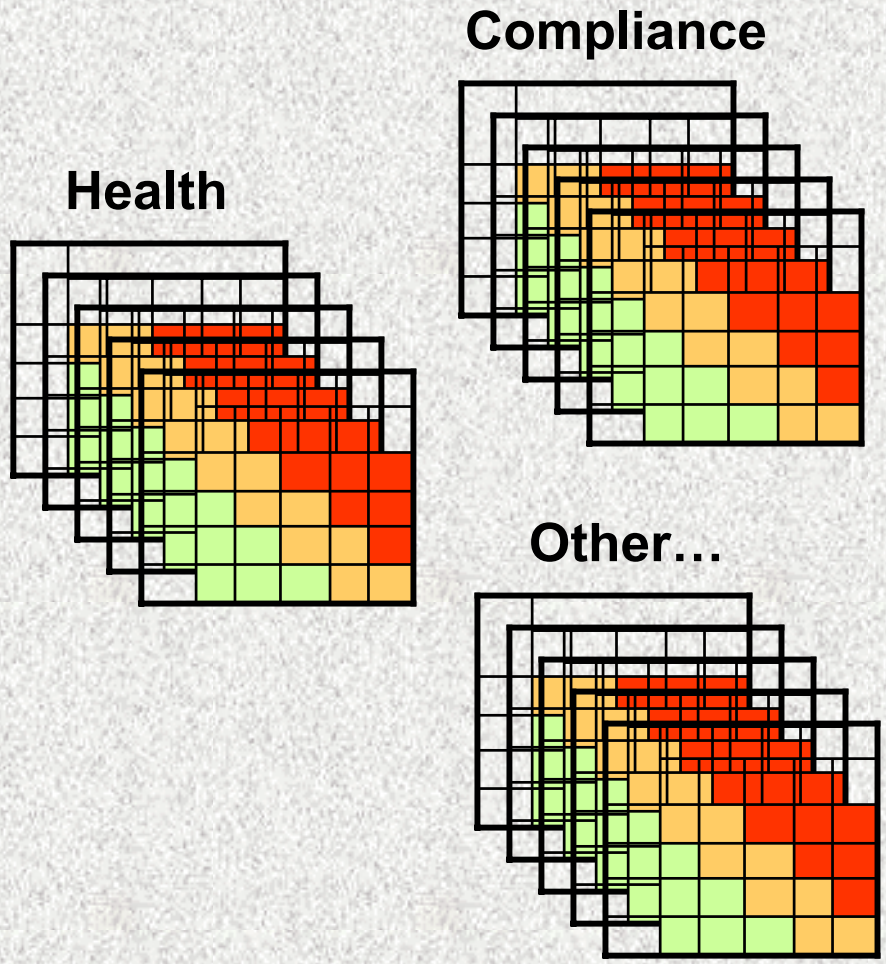




Scored and Prioritized

1. GMP Fault A
2. GMP Fault T
3. GMP Fault C
4. GMP Fault D
5. GMP Fault X
6. GMP Fault M

Risk Ranking & Filtering Model

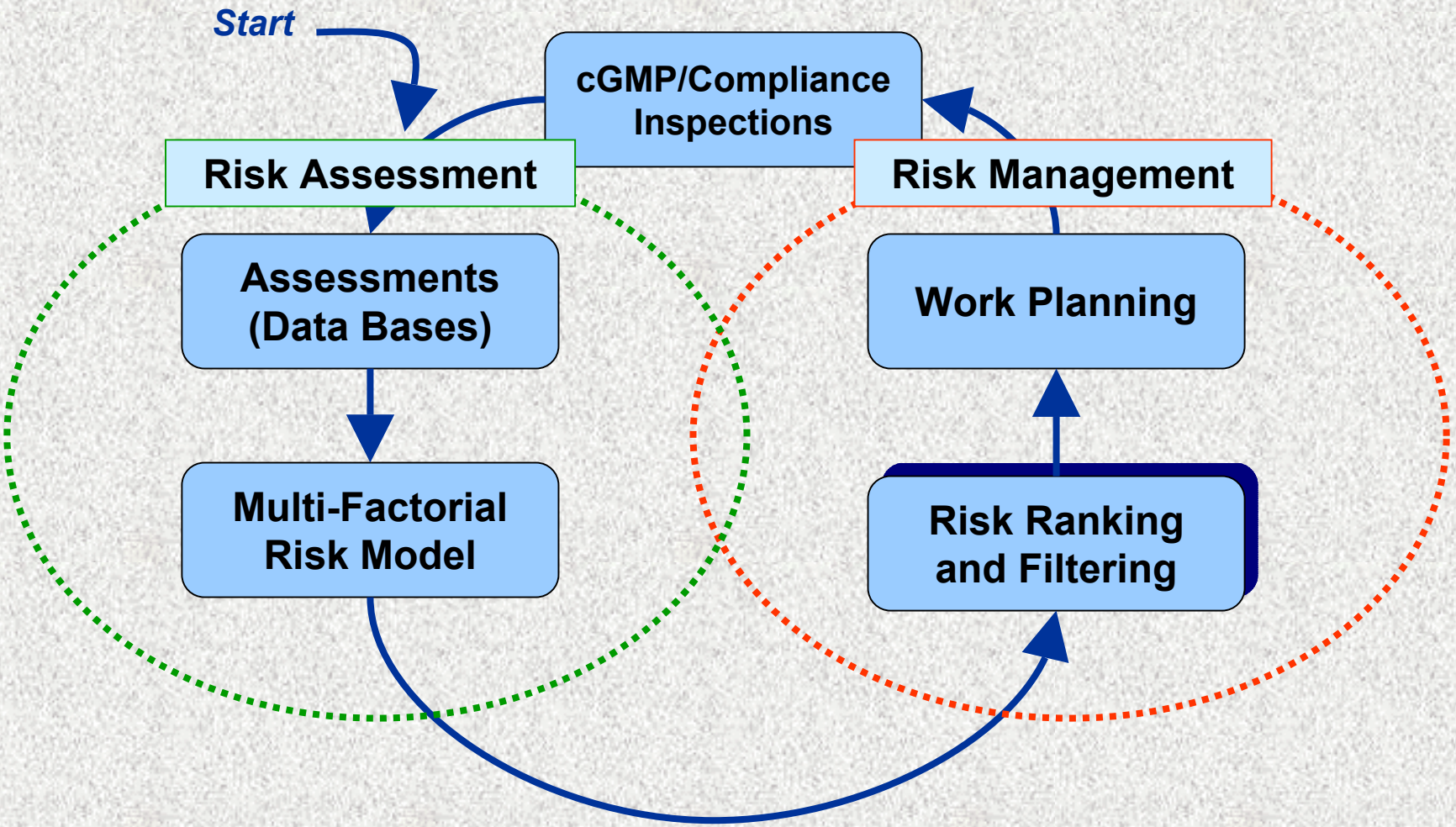


(Risk Ranking and Filtering)

Scored and Prioritized Under Multiple Criteria

1. GMP Fault M
2. GMP Fault T
3. GMP Fault C
4. GMP Fault D
5. GMP Fault X
6. GMP Fault A

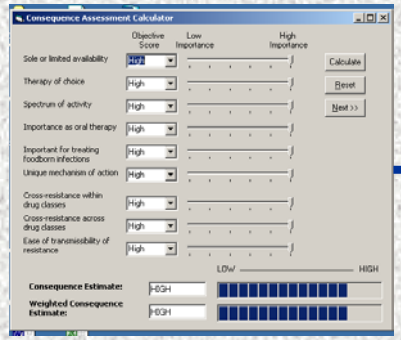
Risk Analysis Cycle



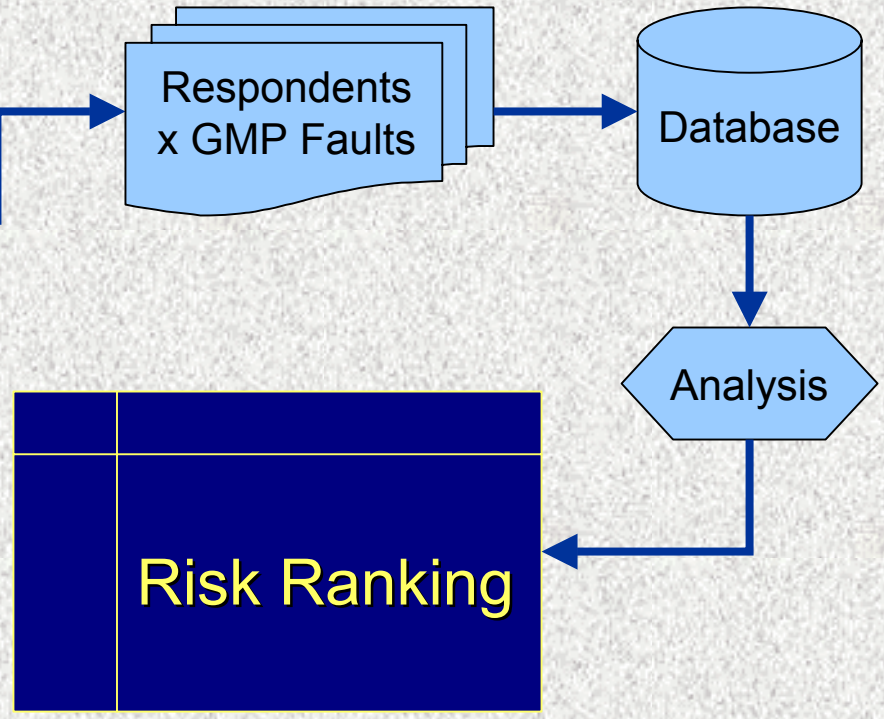
Pilot Scale?

Example Approach to Build RRF List*

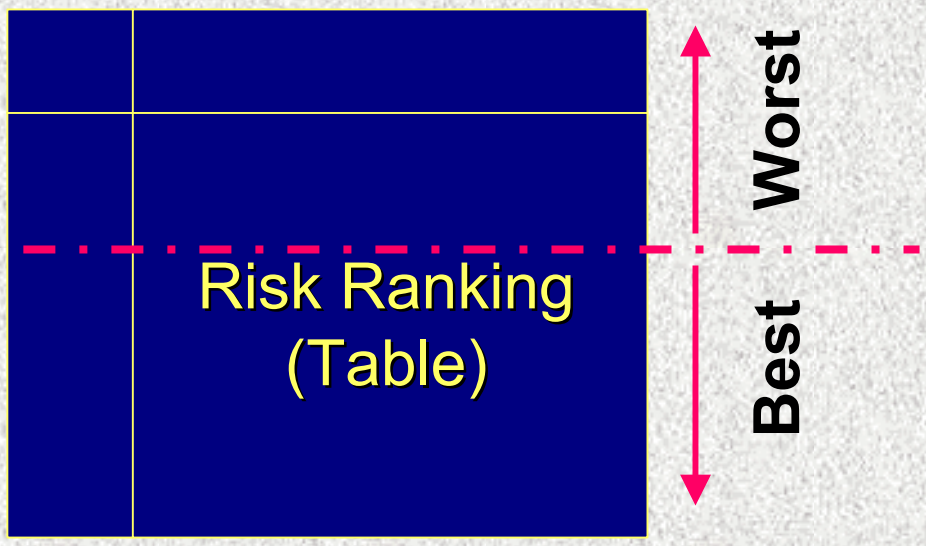
Risk Estimator



- Risk Managers
- GMP Experts
- Sr. Managers
- Industry



Fold into cGMP Model



Risk Management "Cut-Off"

- Budget
- Risk Tolerance
- Benefit-Costs
- Stake holders

Conclusions

- Risk Assessment provides a process for organizing information in support of risk-based decision making.
- Risk assessment is one of the tools available for Risk Management, the activity in which the options for controlling risks are examined in light of costs, benefits and risk trade-offs.
- Multifactor Risk Ranking and filtering approach might be robust enough to employ in the GMP Initiative.