

MANAGEMENT OF BENEFIT:RISK UNCERTAINTIES - FOUNDATIONS FOR CONSIDERATION

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PERSPECTIVES

■ Industry

- ParagonRx
- Reckitt-Benckiser (OTC)
- Alpharma Pharmaceuticals (Brand/Generics)
- Organon Pharmaceuticals

■ Academia

- Johns Hopkins Bloomberg School of Public Health [MPH]
- Rutgers – New Jersey Medical School [MD]

■ Government

- Food and Drug Administration [CSS, DRISK]

■ Medical

- Beth Israel Medical Center [General Surgery]

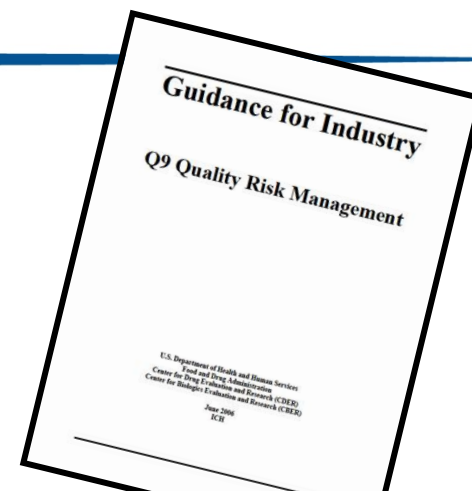
■ Personal

- Son, Parent, Spouse, Patient

BENEFIT AND RISK INVENTORY

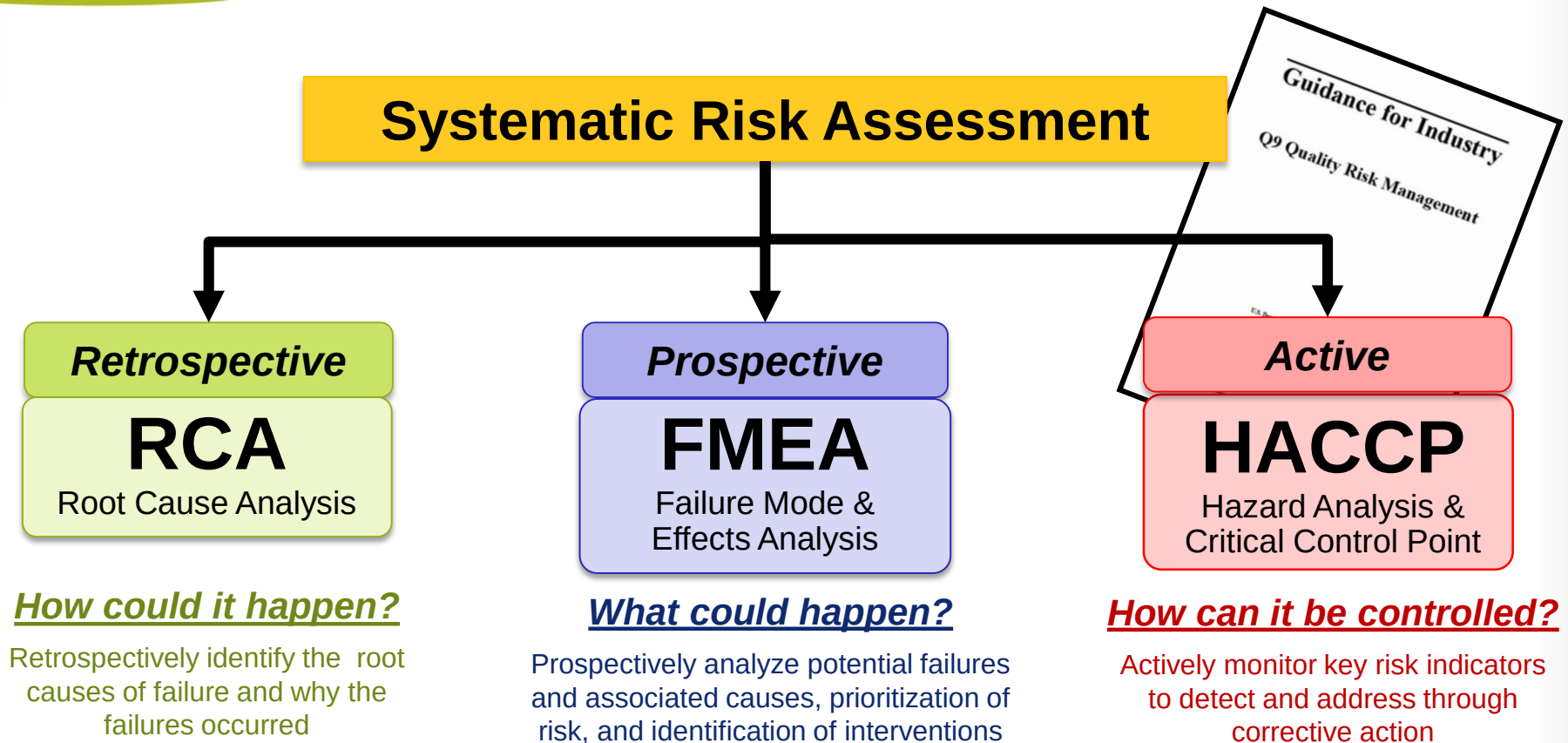
	BENEFIT	RISK
Formatting discussions	ICH E2C PBRER	ICH E2C PBRER
ICH-harmonized detailed framework		ICH Q9: Quality Risk Management
Formalized dictionary for characterization		MedDRA for adverse events
Regulatory surveillance systems		Sentinel, FAERS, MedWatch
Legislative requirement for management		Risk Evaluation and Mitigation Strategy
# of summary sections in a package insert	2 (ind & usage, clinical studies)	8 (ind & usage, contraind, warn & prec, adv rxn, drug inter, use in specific pop, drug abuse, overdose)
# of FDA guidance document mentions	<20 [prelim]	150+

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- 1. USE SYSTEMATIC APPROACHES**
 - 2. ESTABLISH A “BENEFIT” LEXICON**
 - 3. MAP THE REAL-WORLD CONTEXT**



EXPERIENCE OF FDA / ICH Q9 METHODS FOR SYSTEMATIC RISK ASSESSMENT

6



Using the best qualities of three methods from the ICH Q9 Guidance on “Quality Risk Management”

FIVE STEPS FOR PERFORMING A SYSTEMATIC RISK ASSESSMENT



1. Define the risks to be addressed



2. Form a cross-functional team of relevant experts



3. Map the process to be analyzed

	Serious	Major	Minor	Negligible
Very Frequent	25	20	15	10
Frequent	20	16	12	8
Occasional	15	12	9	6
Rare	10	8	6	4
Very Rare	5	4	3	2

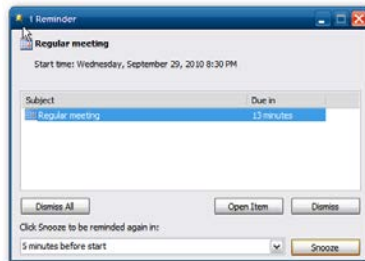
4. Analyze, score, and prioritize risk and interventions



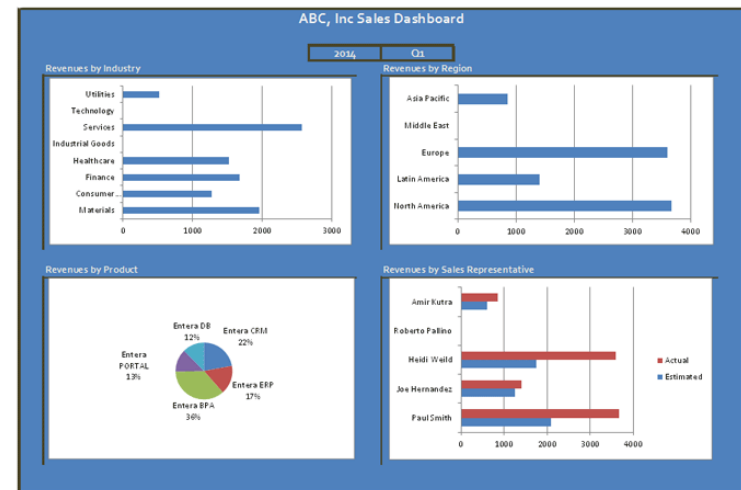
5. Define indicators, thresholds and corrective actions

RISK (OR BENEFIT) CERTAINTIES AND UNCERTAINTIES

“Fixed” (Certainties) Risk Controls

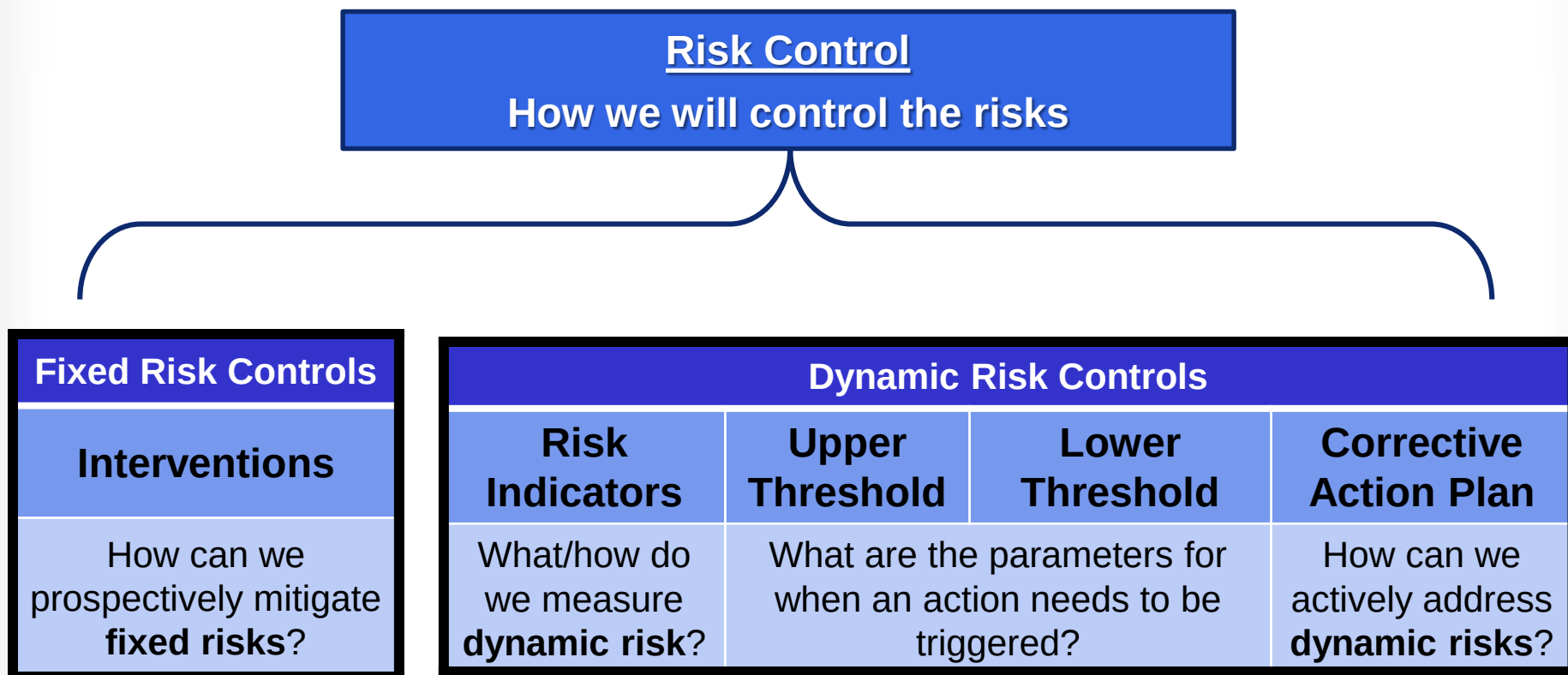


“Dynamic” (Uncertainties) Risk Controls



Risks are managed depending on the “available time” from information-to-hazard

ADAPTING HAZARD ANALYSIS AND CRITICAL CONTROL POINTS (HACCP)



BALANCING THE BENEFIT DISCUSSION

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Benefit Management?		• Provisions for improved patient access • Tools for optimizing patient outcomes • Structured benefit communications • Surveillance tools for non-approved uses • Additional post-marketing efficacy studies • Exploration of additional indications • Exploration of next-generation variations • Stakeholder support tools and materials
Risk		
Risk Management		
Benefit-Risk Summary Assessment		



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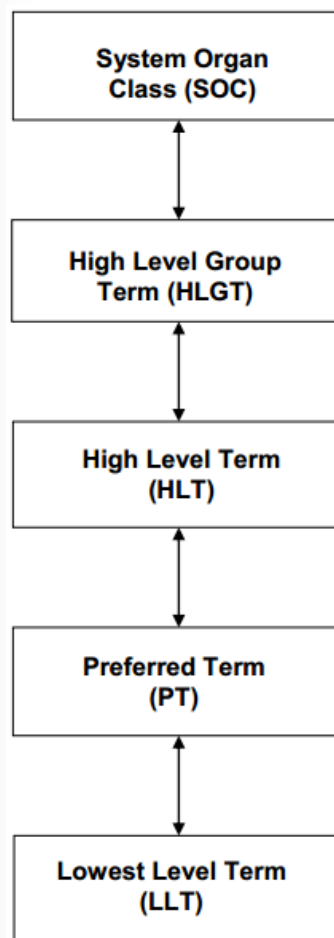
3. MAP THE REAL-WORLD CONTEXT

SIDE-BY-SIDE PROTOTYPE OF B:R TABLE¹² FOR EFFICIENT HCP COMMUNICATION

Benefit Classification (N=465) Preferred Term		System Organ Class (N=465) Preferred Term n (%) ¹	
Overall		Any Related AE	288 (61.9%)
Improvements in QOL	337 (72.5%)	Gastrointestinal disorders	219 (47.1%)
Improvements in ADL	321 (69.0%)	Constipation	145 (31.2%)
Improvements in mobility	150 (32.0%)	Diarrhoea	10 (2.2%)
Symptom Changes		Dry mouth	17 (3.7%)
Decreased acute pain	395 (85.0%)	Nausea	103 (22.2%)
Measurements		Vomiting	37 (8.0%)
Decreased pain score by >3 of 10	150 (32.0%)	General disorders and administration site conditions	51 (11.0%)
Increased 5-year survival rate	186 (40.0%)	Fatigue	19 (4.1%)
Decreased hospital length of stay	223 (48.0%)	Nervous system disorders	99 (21.3%)
Reduction in relapse rate	250 (53.8%)	Dizziness	19 (4.1%)
Biomarkers		Headache	32 (6.9%)
[Stress lab value increase]	75 (16.0%)	Somnolence	34 (7.3%)
		Psychiatric disorders	42 (9.0%)
		Anxiety	10 (2.2%)
		Insomnia	13 (2.8%)
		Skin and subcutaneous tissue disorders	52 (11.2%)
		Hyperhidrosis	16 (3.4%)
		Pruritus	26 (5.6%)

**Efficient formatting for easy HCP communication
and decision-making**

MedDRA FOR RISK: CAN IT BE EXPANDED FOR “BENEFIT”?




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Could MedDRA be modified to include a standardized “benefits” lexicon so we can have easy-to-read tables?

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CONTEXT MATTERS, THE LAST MILE OF INDIVIDUAL CONTEXT NEEDS DETAIL

15

**Sponsors and
Regulators**

Product Development Benefit:Risk

PATIENT

- Progression of disease
- Experience of failed therapies
- Change in coverage

PHARMACIST

- Dispensing restrictions
- Special dispensing reqs
- Complex REMS

PRESCRIBER

- Frequent rejections
- Poor single experience
- Complex guidelines

PAYORS

- Increasing off-label use
- Higher upfront costs
- Sicker patient population

INSTITUTIONS

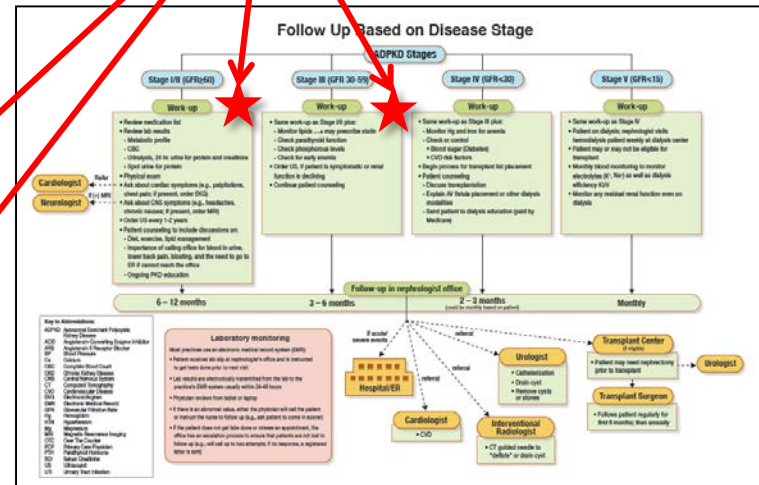
- Indigent care burdens
- Emergency room utilization
- Prolonged stays

ETHNOGRAPHY: STAKEHOLDER MAPPING OF REAL-WORLD EXPERIENCE

Methodology consisting of on-site clinical observations of the practices and behaviors of healthcare providers in their environment to provide deep insights about the patient care process



Ethnography identifies what people actually do versus what they may say they do in interviews or focus groups



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CONSIDERATIONS

1. Incorporate the lessons learned of “systematic approaches” from “risk management” for “benefit management” in future regulations, guidances, and tools
2. Adapt MedDRA to accommodate for simpler and more efficient “benefit” communication
3. Encourage use of ethnographic mapping methods to better understand individual stakeholder context