ICH Q9 – An Industry Perspective: Ensuring Quality to Patients in a *Risk-Based* Regulatory Environment

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Presentation Overview to Convey Challenges & Opportunities of ICH Q9

- **Quality Risk Management – Not A New Concept**
  - Historical review of "Risk-Based" guidance documents
  - Expectations for "control of risk" based on knowledge shared
- **Basic Principles of ICH Q9**
  - Developing an appreciation for terminology and linkage to ICH Q8
- **Focus On What is "Critical to Quality" – New Concept?**
  - Target Product Quality Profile as basis for *Criticality Analysis*
  - Relationship between Normal Operating & Proven Acceptable Range
  - Control strategy based what is "critical to quality"
- **Closing Thoughts**

"Risk is Inversely Related to Knowledge"

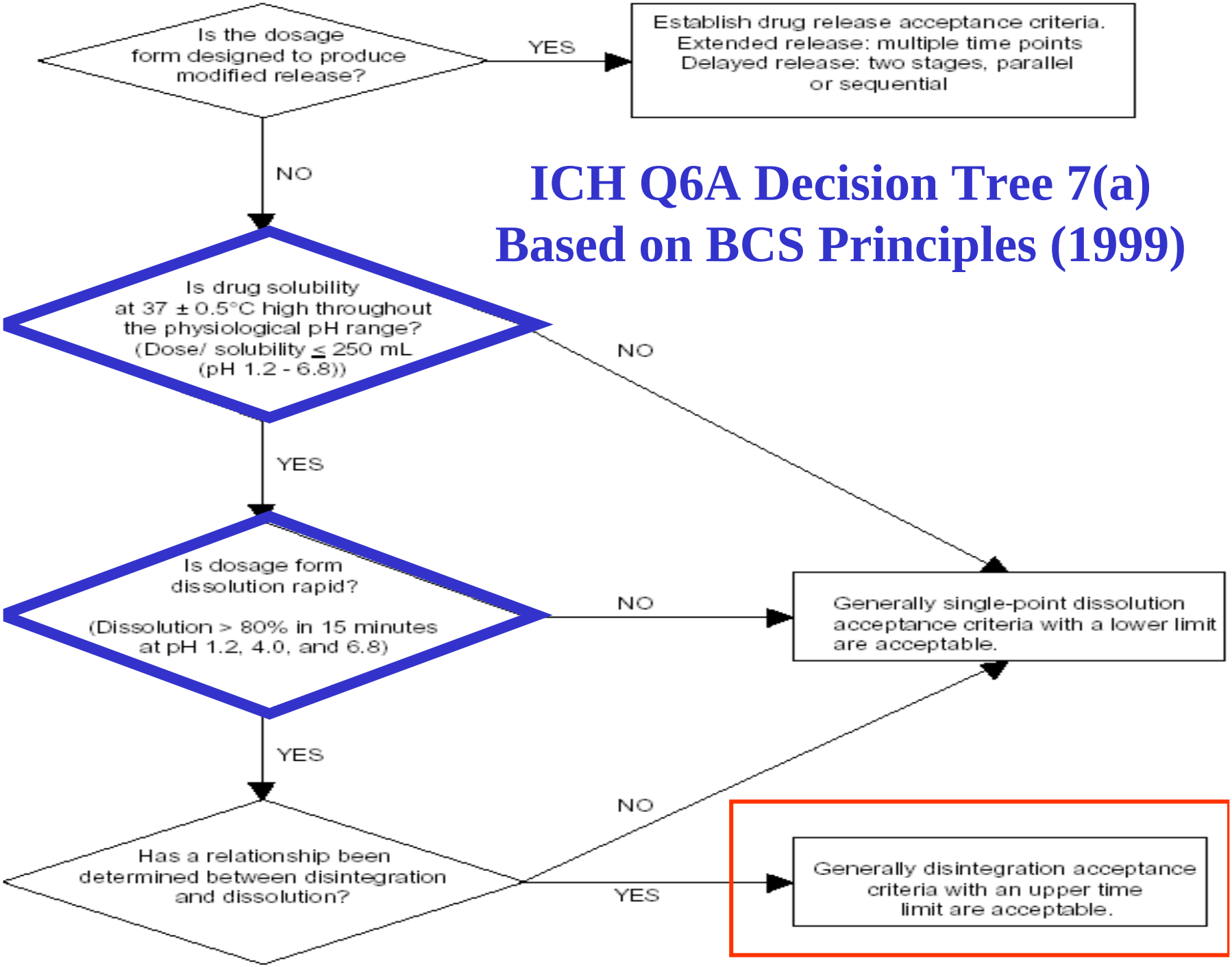
- Compliance history
- Type of drugs manufactured at facility
- Specific manufacturing processes
- ICH Q9 (November 2005)

- Level of product and process understanding acquired AND shared
- Dosage Form Design
- Process Design
- ICH Q8 (November 2005)

SUPAC – A Landmark of "Risk-Based" Guidance Document

- *Scale Up & Post Approval Changes* – 1995
- Limit **RISK** of change based on product **KNOWLEDGE**
- Impact of product/process changes are not same for all drugs
  - Recognizes importance of solubility & permeability
    - **B**iopharmaceutical **C**lassification **S**ystem
- Regulatory requirements based on **KNOWLEDGE** shared
  - Comparative dissolution rather than bioequivalence testing possible if required criteria are met

ICH Q6A Decision Tree 7(a)
Based on BCS Principles (1999)



ICH Q3A & 3B: Issued in 1995 and 1996 Employing *Risk-Based* Approach

- Guides Sponsor's Control strategy for impurities
  - Scientific knowledge (ICH Q8)
    - Process capability for drug substance & product
      - Sets "**N**ormal **O**perating **R**ange"
  - Risk Management (ICH Q9)
    - Thresholds set by reported levels of impurity
      - Potential impact on Safety **and** Efficacy
    - Qualification sets "**P**roven **A**cceptable **R**ange"

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Maintaining *Quality* Throughout Product Life-Cycle Minimizes 'Risk'

- "No drug is free of risk" – Pharmacy 101
- Maintain product *quality* across product life-cycle
  - Benefit AND Risk to patient is not significantly different than that observed in the clinical program
- Effective 'Risk management' provides
  - Proactive means to identify and mitigate potential quality issues
    - Earliest stages of product development
    - Appropriate use of control strategy
  - Improve decision making if quality problem occur

What is RISK and Associated Harm? Key Terms to Understand

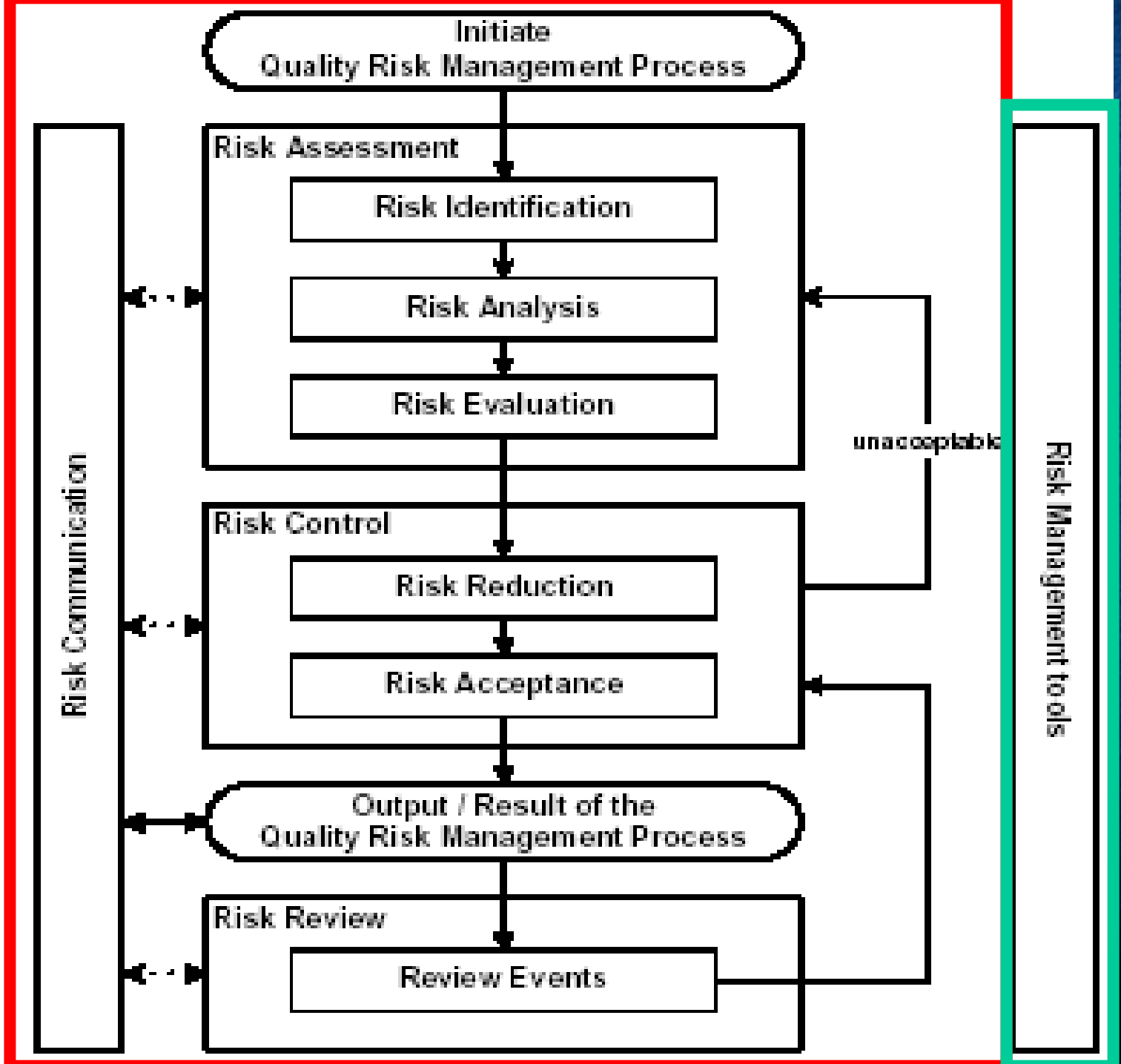
- Risk
  - "The combination of the probability of occurrence of harm and the severity of that harm"
- Harm
  - "Damage to health, including the damage that can occur from loss of product quality or availability".
- Hazard is defined as "potential source of harm"
  - Hazard is identified as knowledge shared in Pharmaceutical Development Report (ICH Q8)
    - What can go wrong?

‘Risk’ Is Ultimately Defined By Impact on Stakeholder

- Variety of stakeholders assessing ‘Risk’
  - Patients
  - Medical practitioners
  - Regulatory agencies
  - Industry
  - Etc….
- Based on same Hazard, different ‘stakeholders’ may
  - Identify different potential harms
  - Place different probability on each harm occurring
  - Experience different severities of the harm

‘Quality Risk Management’ Process

- “ Risk management is a systematic process for the identification, assessment, control AND COMMUNICATION of risks to the quality of pharmaceuticals across the product lifecycle. Level of effort, formality and documentation of the risk management process should be commensurate with the level of risk.”
- ICH Q9 focuses on RISK
  - Assessment, Control, Communication and Review
- Risk Identification beyond scope of guidance
  - Understanding & Control of ‘Hazard’ linked to ICH Q8


Initiate
Quality Risk Management Process
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
Risk Control
Risk Reduction
Risk Acceptance
Output / Result of the
Quality Risk Management Process
Risk Review
Review Events
Risk Communication
unacceptable
Risk Management tools

Foundation of Risk Management Linked to Desired Outcome(s)

- Target Product Quality Profile
  - First step in *Quality by Design*
  - Developed by multi-functional team
  - Focus on intended Package Insert
    - Start at the End and work to the Beginning
  - Must be consistent with post-approval change
  - Define what Quality Attributes and related Process Parameters are essential and needed to be controlled to ensure consistently reliable performance in clinic and marketplace

Considerations In Development of Target Product Quality Profile For Drug Product

Indications and Usage	Use in Specific Populations • *Pediatric Use* • *Geriatric Use*
Dosage and Administration	Drug Abuse and Dependence
Dosage Forms and Strengths	Description
Pharmacology • *Pharmacodynamics* • *Pharmacokinetics*	How Supplied/Storage and Handling

Target Product Quality Profile: What Must be Achieved To Reach End

- Critical Quality Attributes (CQA) = "Outputs"
  - A physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality (ICH Q8(R) Step 1 Draft 7.0)
  - May form basis for proposing Specifications
- Immediate Release Oral Solid Tablet
  - Potency
  - Dissolution **or** Disintegration requirements
  - Water Content **if** susceptible to hydrolysis
  - Polymorphic form in drug product
  - Etc…

Target Product Quality Profile
How to Ensure Desired End is Reached

- Critical Process Parameter (CPP) = “Inputs”
  - A process parameter whose variability impacts a quality attribute and therefore needs to be controlled to ensure the process produces the desired quality. A critical process parameter remains critical even if it is controlled. (ICH Q8(R) Step 1 Draft 7.0)
    - Manufacturing operation steps (e.g. drying time)
    - Materials
      - API, Excipients, Packaging
    - Analytical methods
    - Environment
    - People
    - Etc

Cause& Effect Diagram One Tool to Assess Knowledge & Sources of "Risk"

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Prioritization Matrix Constructed

Quality Attributes	Blend Time	Lube Time	API Surface Area	Pre-Compression Force	Compression Force	Compressing Speed	Feed Frame Setting	Excipient Particle Size	Importance
Dissolution	1	7	9	1	9	1	3	1	**10**
Assay/ Potency	1					5	3		**10**
Uniformity	7	1	9			5	3	5	**10**
Appearance	1	3			3	3			**5**
Stability			1		3				**7**
Yield						3			**3**
Ranking Total	**95**	**95**	**187**	**10**	**126**	**134**	**90**	**60**	
Percent	**13**	**13**	**25**	**1**	**17**	**18**	**12**	**8**	

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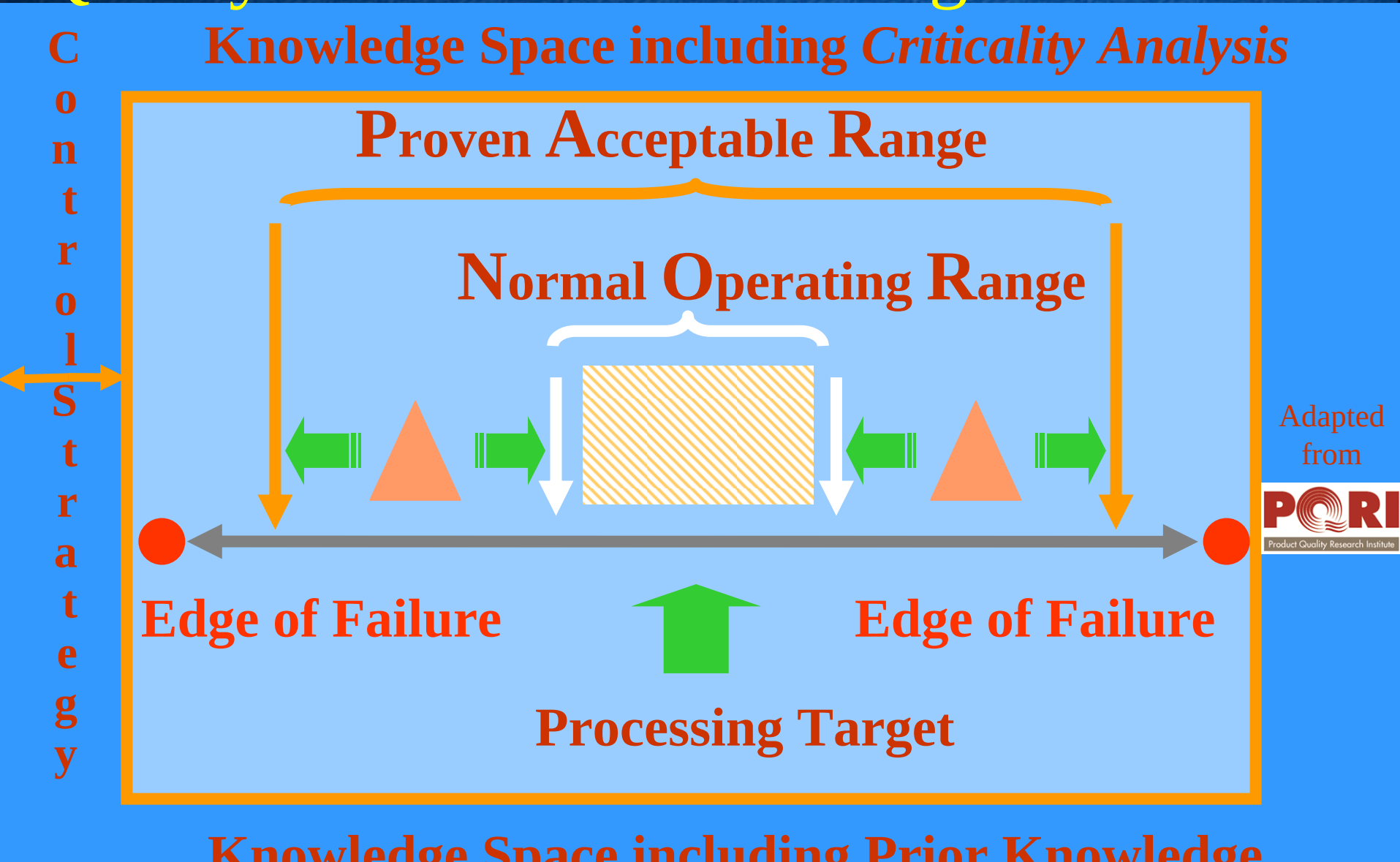
Consider When Surface Area is a Critical Quality Attribute of the Drug Substance …



Adapted from

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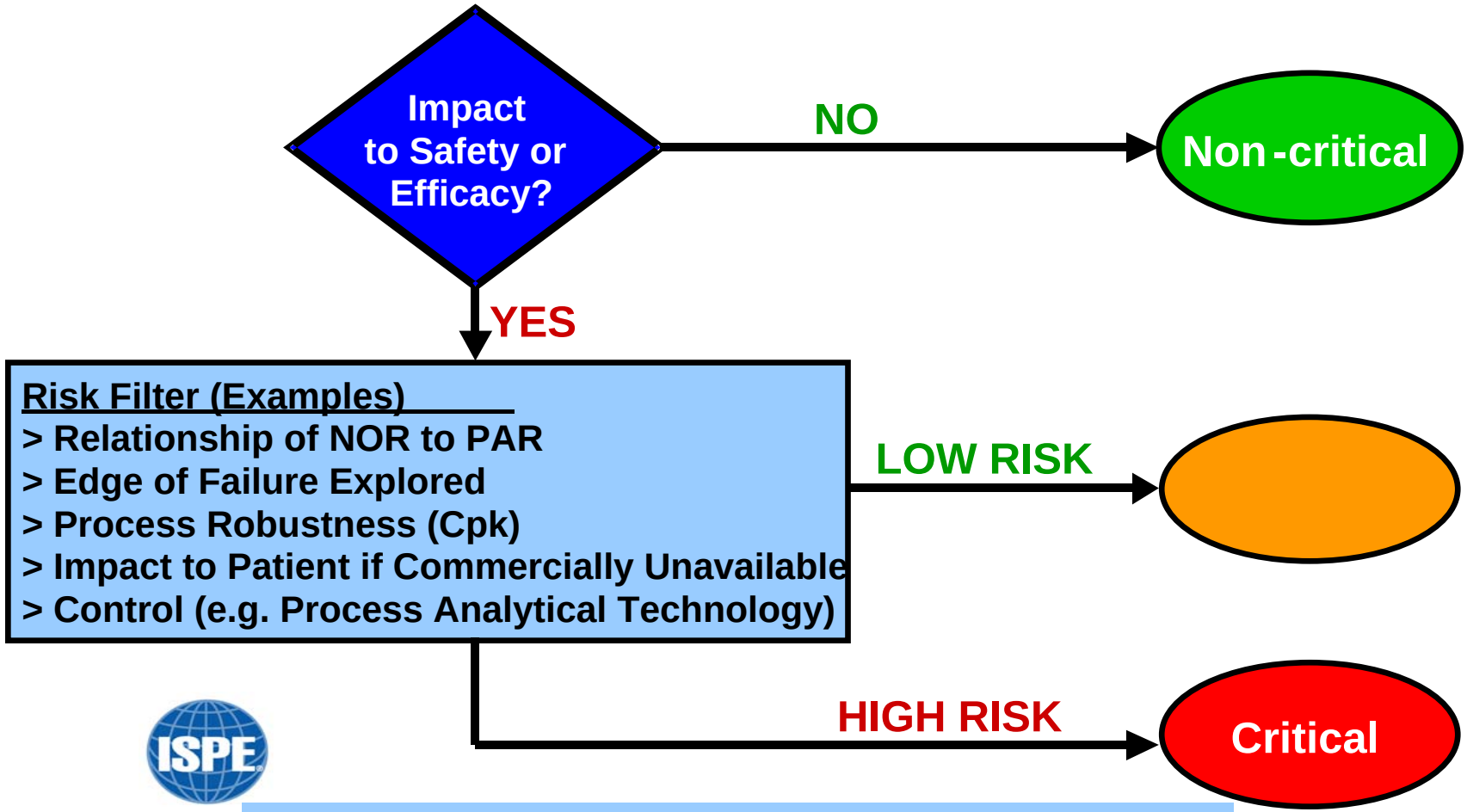
Scientists from Around the World Working to Define "Criticality"

Critical vs. Non-Critical Attributes & Parameters



Draft Output from Washington, D.C. - June 2007

Imaginary Example Describing "Risk Management" Process

- A scientist in the Quality Assurance laboratory of *Company XYZ* confirmed that the stability of the company's new antibiotic has marginally passed the Potency specifications after 12 months of storage at 30°C/75% RH. The product is now 91% of Label Claim. The primary mechanism of degradation is known to be hydrolysis. The degradation product is also approaching the specification limit and has been shown to be an inactive metabolite. Although packaged in an aluminum blister, it appears that the seal has failed.
- Team may construct a Cause and Effect Diagram

Three Primary Considerations During Assessment Phase of 'Risk Management'

- Must fully understand what is considered to be :
  1. 'Hazard' – What went wrong?
  2. 'At risk' – What is the general consequence?
  3. 'Harm' – What is the probability and severity that a stakeholder will be affected by the hazard?
- *Company XYZ* defines "Risk"
  - Hydrolysis due to package failure = 'Hazard'
  - Reduction of product potency/purity = 'At Risk'
  - Potential lack of efficacy = 'Harm' to patient
  - Potential product recall = 'Harm' to industry
  - Potential public criticism for lack of oversight = 'Harm' to regulatory agency

Three Control Choices Available When Deciding on Management of Risk

1. ***Risk mitigation***
   - Focuses on a reduction of severity of harm
   - Limits negative consequences of particular event
     - *Company XYZ* cannot change inherent property
2. R***isk reduction***
   - Focuses on reduction of probabilities of harm
     - *Company XYZ* corrects cause of package failure
3. ***Risk acceptance***
   - No additional risk control activities necessary
     - Must be supported by upper management
     - Not an viable option in most cases

Example of Risk Management as Part of Regulatory Activities

"An effective quality risk management approach can further ensure the high quality of the drug product to the patient in providing a proactive means to identify and control potential quality issues with the product during development and manufacturing. Additionally use of quality risk management can also improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions and may provide regulators with greater assurance of a company's ability to deal with potential risks and may beneficially affect the extent and level of direct regulatory oversight."

- Both a CHALLENGE & OPPORTUNITY for all

Closing Thoughts From A Personal Perspective

- *Risk-Based* regulatory environment is not new

Stakeholder	Challenge	Opportunity
Health Authority	• Presentation of more scientific interpretation of data by sponsor in assessing risk (ie Criticality report) • Recognition of *risk-based* concepts consistent with Q8 & Q9	• Focus resources on what is "critical to quality" • Reliable supply of medicines to citizens
Industry	• Potentially longer time to filing new drug application • Potential for significantly different specifications world-wide based on unpredictable acceptance of "risk-based" control strategy by HAs	• Control strategy based solely on "critical to quality" • Innovation across product life-cycle

THANK YOU for your kind attention. We look very forward to hearing your thoughts regarding Challenges and Opportunities associated with implementation of ICH Q9 during the Panel Discussion as well as your active participation in helping define the future of “Quality Risk Management”