Risk Analysis and Mitigation in Drug Product Development and Technology Transfer

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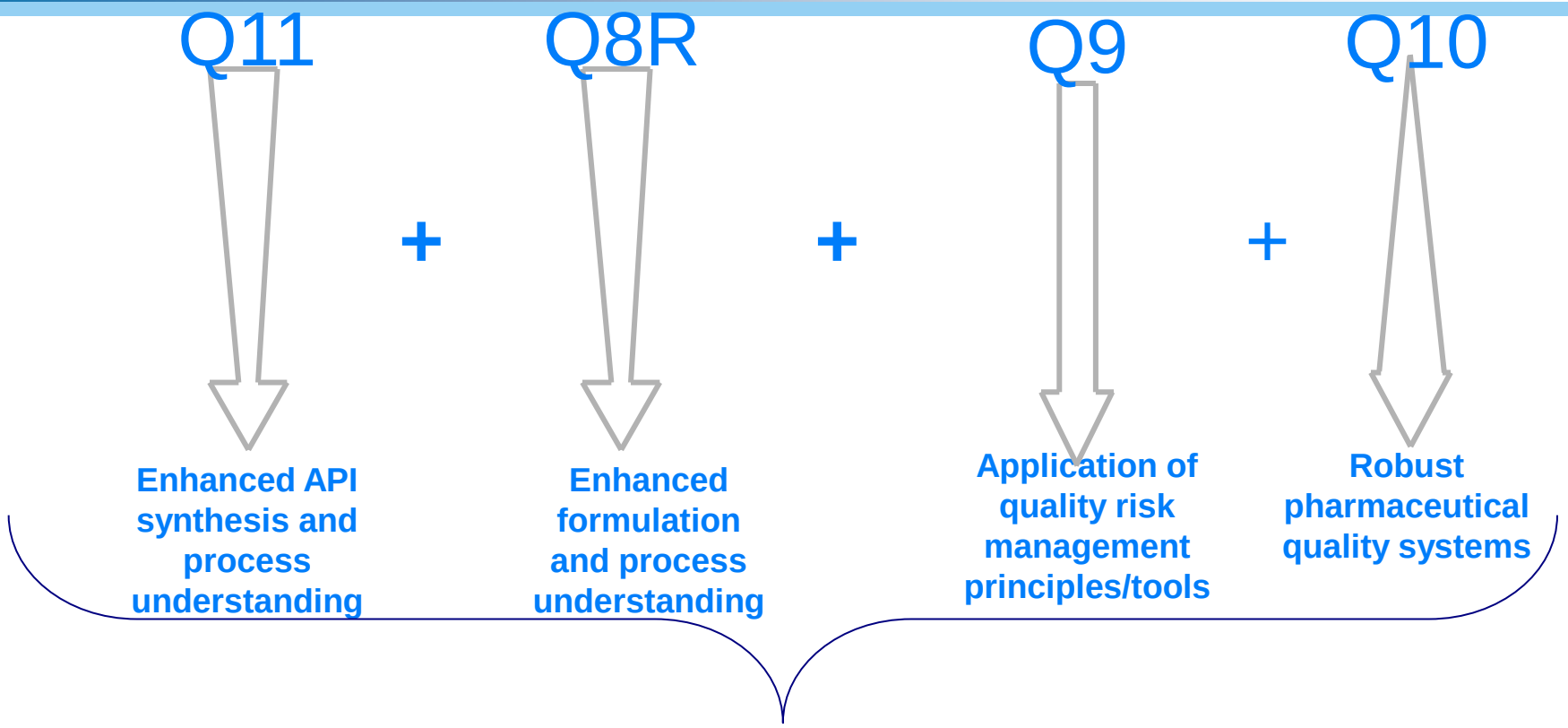
The ICH Vision & Opportunity

Pharmaceutical Development: (QbD) Q8 & Q11 + *Quality Risk Management* (QRM) Q9 + Modern Effective *Pharmaceutical Quality Systems* Q10

A New Quality Paradigm

- ✓ Science and risk-based approaches to product development, dossier submission, review, inspection, and post-approval change management
- ✓ Manufacturers empowered to effect continuous improvement and technical innovation throughout the product lifecycle
- ✓ Efficient and consistent regulatory oversight across/between regions

Quality by Design Concepts: "ICH Quartet" of Guidance Documents



Combination of ICH Quartet → Quality by Design

- Decrease Variability
- Assure market supply
- Faster change implementation
- Science support quality investigations

Benefits

- Lower Risk Operation
- Innovation
- Continual Improvement

- Reduce COG
- Streamline regulatory reviews (S&E)
- Framework for decreased regulatory burden

“High Level Risk Assessment”

Drug Product Quality Attributes			FA7	FA6	FA5	FA4	FA3	FA2	FA1
		Limit If Tested	Encapsulation	Extragranulator Lub	Extragranular Blend	DG Roller Compact & Mill	Intragranular Lub	Blend & Mill	Excipient Blend
Dissolution									
Potency									
Purity (Impurities)									
Content (Weight) Uniformity									
Appearance									
Stability	Physical								
	Chemical								

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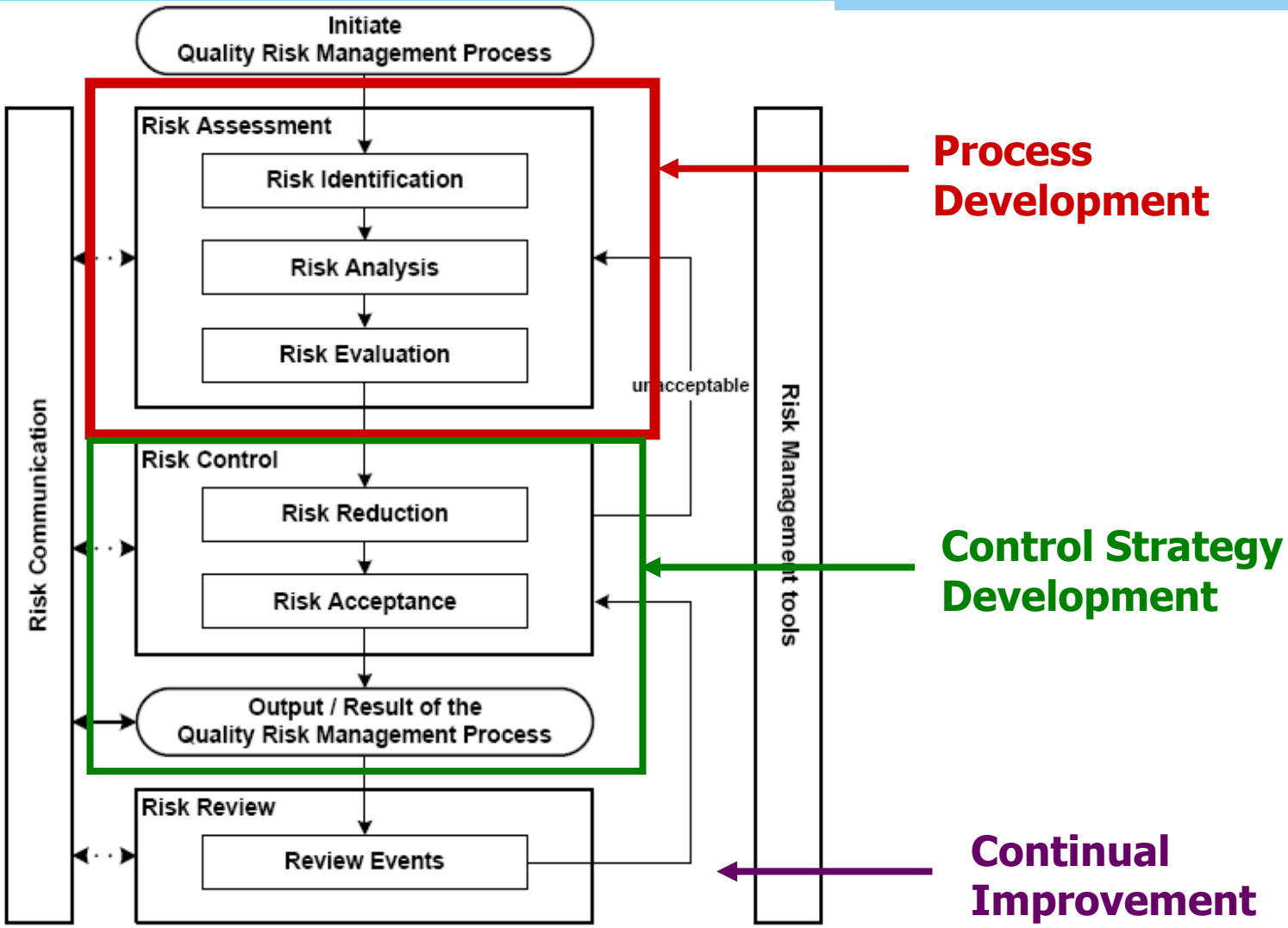
Quality Risk Management Process (Q9)



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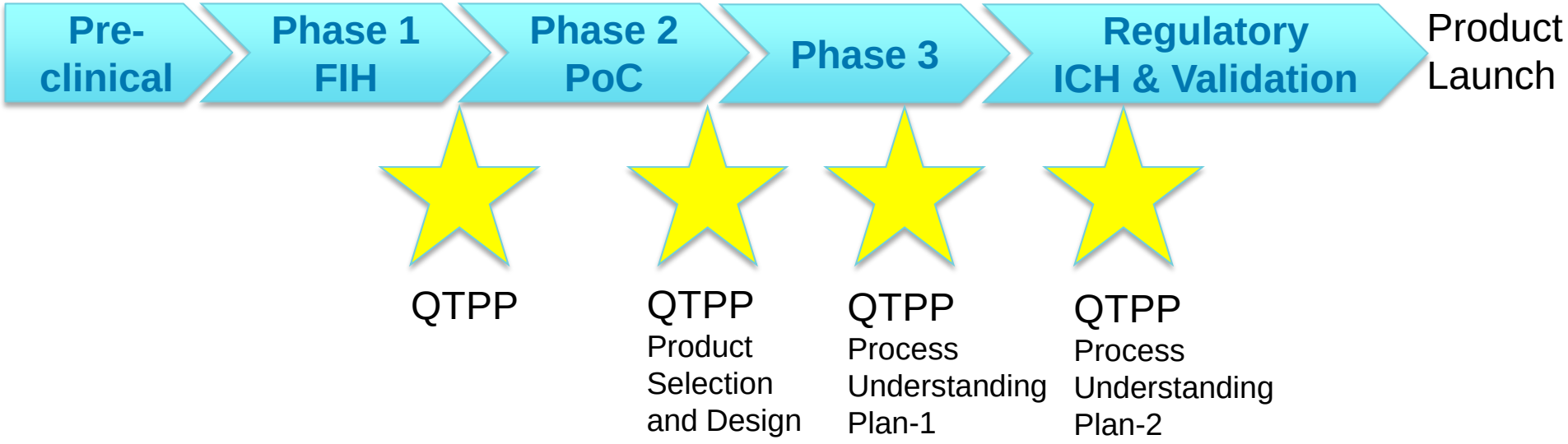
"Customer Perspective"

- **Amount of time that we actually spend processing is small versus the time that we spend on the ancillary activities – typically <10% time is actual VA time.**
- **A robust process reduces the time required on ancillary activities because:**
  - Less Quality Action Reviews (QARs)
  - Less safety incidents
  - Less process issues requiring investigation
  - Lends itself to standardisation which is the platform for continuous improvement
- **Well defined Critical Process Parameters and process understanding is the biggest enabler of robust products and process with few ancillary activities.**

Integration of Risk Management with Knowledge Management

- **“Early experience with Quality Risk Management (QRM) taught Pfizer that risk assessments provided a solid foundation from which to build a robust knowledge management infrastructure for product knowledge.”**

Pfizer conducts Risk Assessments during Drug Product Development



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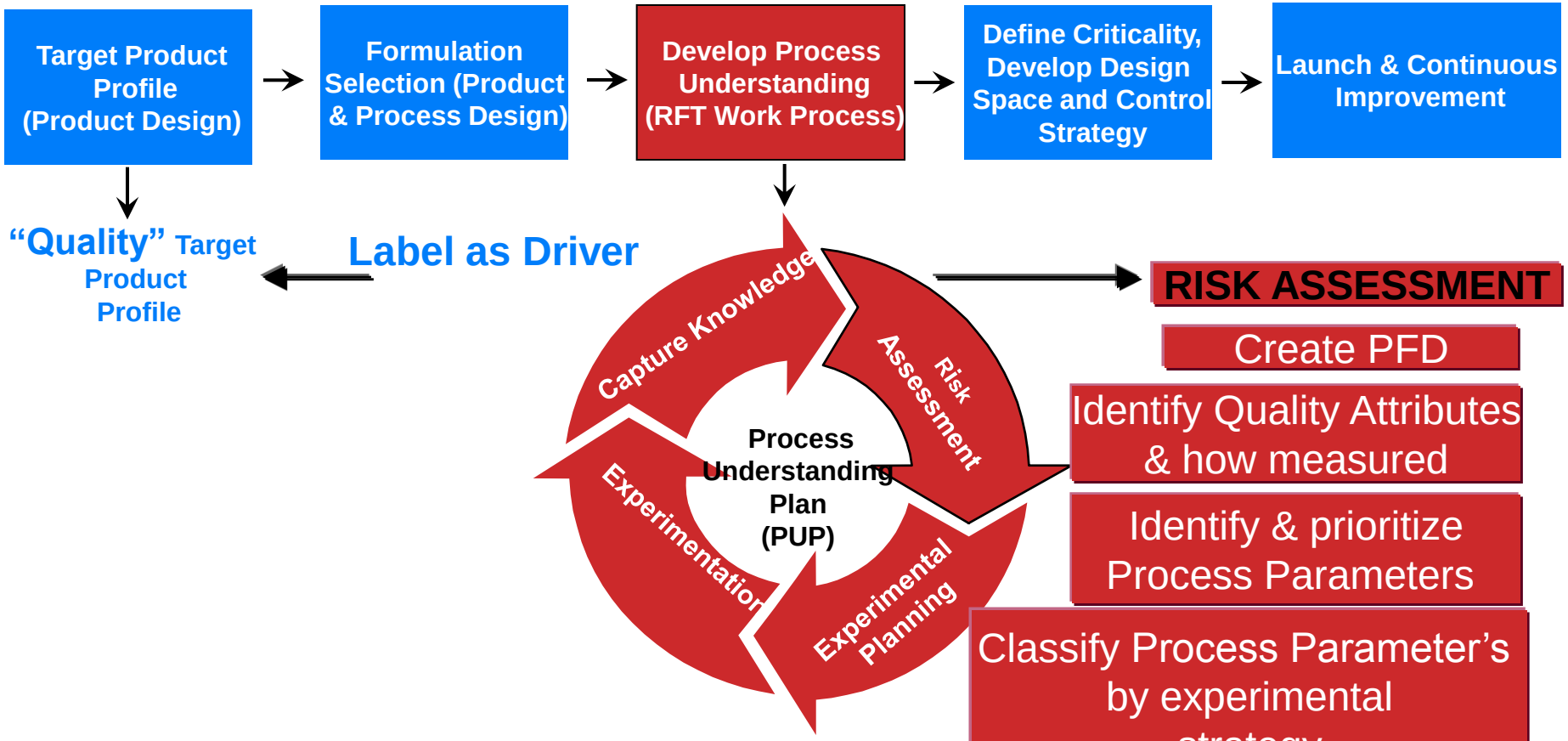
Quality by Design Concepts: Pfizer Overview



Yellow font = completed during pre-work

Quality Target Product Profile

Target Product Profile

Product Attribute	Product Requirement	Design Elements	Potential CQAs
Dosage Form	Suitable for pediatric patients	Sprinkle dosage form with free flowing, filled in a hard capsule size 1	Median bead size
Dose	10mg, 20mg	One formulation for all dose strengths	Potency , Content Uniformity
Mode of administration	Oral, once-daily dosing (CR)	CR film coating on beads to enable once-daily dosing	Dissolution
Shelf life	Not less than adult dosage form (≥ 2 years at 25○ C/60% RH) Same packaging as adult form	Optimal drug: excipient ratio Packaging: HDPE bottles or blister	Moisture, Degradants, Impurities
In vivo Performance	Same in vivo performance as adult No food effect	CR film coating on beads to enable once-daily dosing, IVIVC methods	Dissolution, Bioequivalence
Pharmacopoeia compliance	Meets Pharmacopoeia requirements for oral solid dosage forms	Conventional excipients (USP, Ph Eur, JP) and manufacturing process	Identity, Microbial

Risk Assessment Decision Analysis

Formulation Design

		Dosage Form						
	Product Attributes	Tablet	Mini Tablet	(Oro) Dispersible Tablet	Chewable Tablet	Multiparticulates ("Sprinkles")	Oral Suspension	Oral Solution
Dosage Form	Patient Age	Variable from approx. 7-8 yrs	Single uncoated mini tablet from 6 months [10]	From birth if suspended in small volume of liquid	From Approx. 2 yrs [11]	From 6 mo - 1 yr (when child is able to accept lumpy foods)	From birth	From birth
	Taste Masking Probability of Success	High	High	Medium	Low-Medium	High	Medium (Dependency on API taste threshold and solubility)	Low
	Suitablility for Modified Release	Yes	Yes	Limited	Limited	Yes	Limited (Via complex technologies, e.g. ion exchange resins)	No
	Potential for Platform Technology	Yes	Yes	Yes	Yes	Yes	No (Dependency on API properties)	No (Dependency on API properties)
Dosing and Administration	Dose Flexibility	Limited (Via score lines)	Yes	Limited (Via score lines)	Limited (Via score lines)	Yes	Yes	Yes
	Dosing via NG Tube	Crushed	Crushed	Yes	Crushed	Yes - Depending on size of granuales	Yes	Yes
	Administration	May require crushing or dividing	May require administration mixed with food. May be chewed - impact on taste?	Can be dispensed in a small amount of liquid or dissolved in mouth	Choking or aspiration are a risk in young children but were found to be rare [11]	May be dosed directly into the mouth, sprinkled onto food, or delivered in a capsule	Dosed using measuring cup, spoon or oral dosing syringe. Dose volume is critical.	Dosed using measuring cup, spoon or oral dosing syringe. Dose volume is critical.
	Device / Pack	Blister pack / bottle	Stick pack, sachet, capsule, etc. Dispenser / counting device may be required.	Blister pack	Blister pack / bottle	Stick pack, sachet, capsule, etc.	Bottle, single dose sachet	Bottle, single dose sachet

Decision

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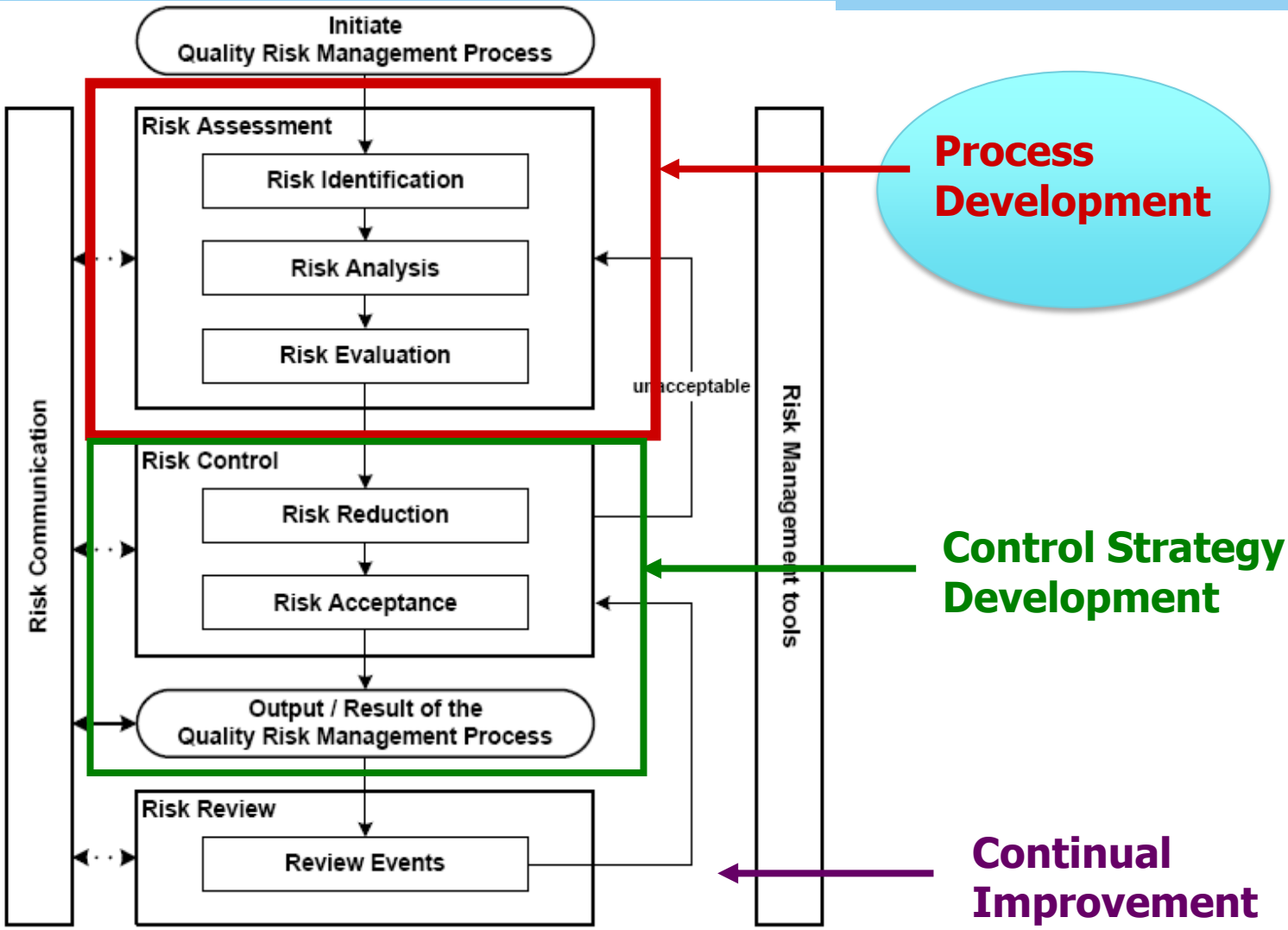
Quality Risk Management Process (Q9)



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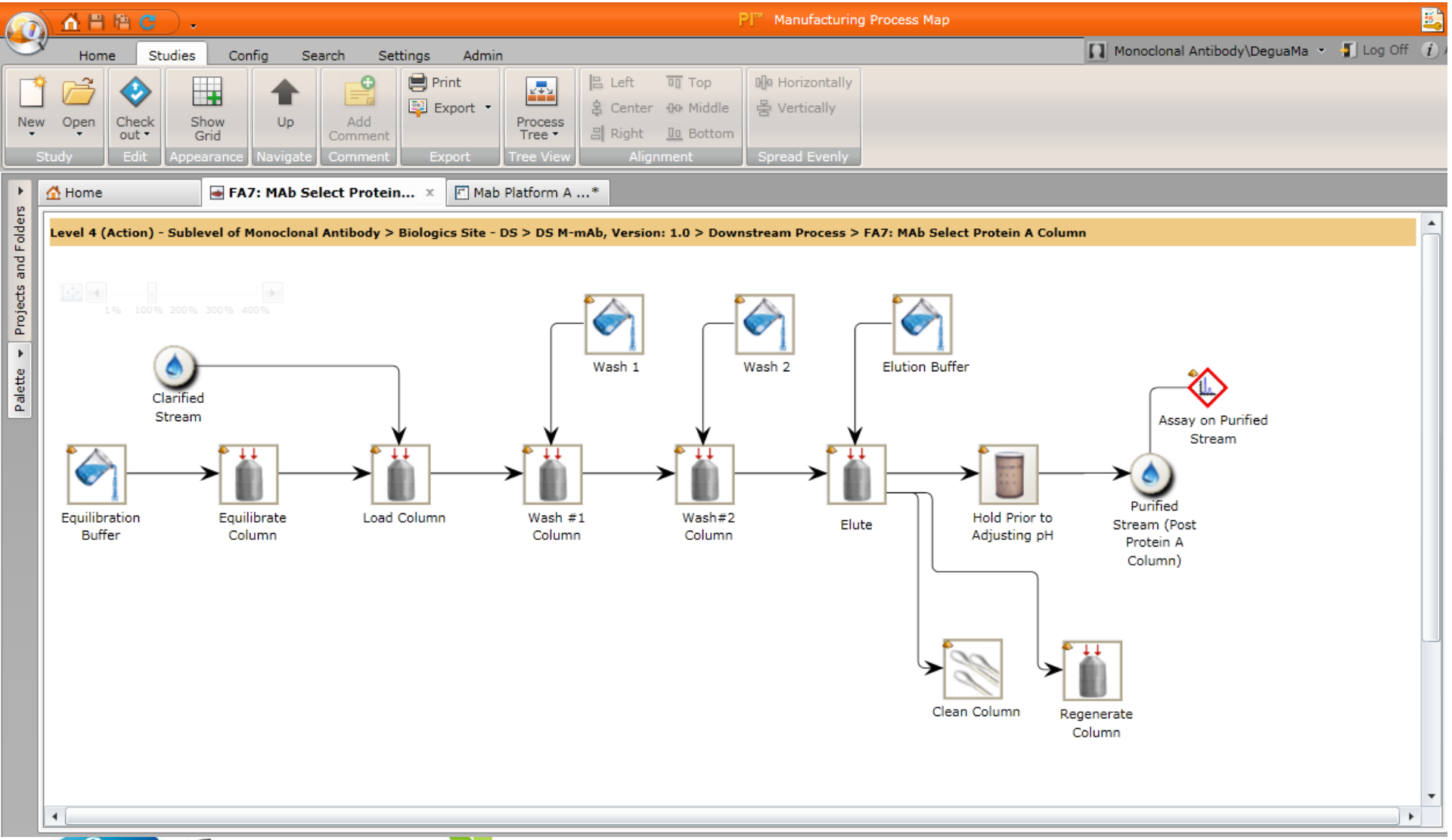
PFD (Process Flow Diagram)



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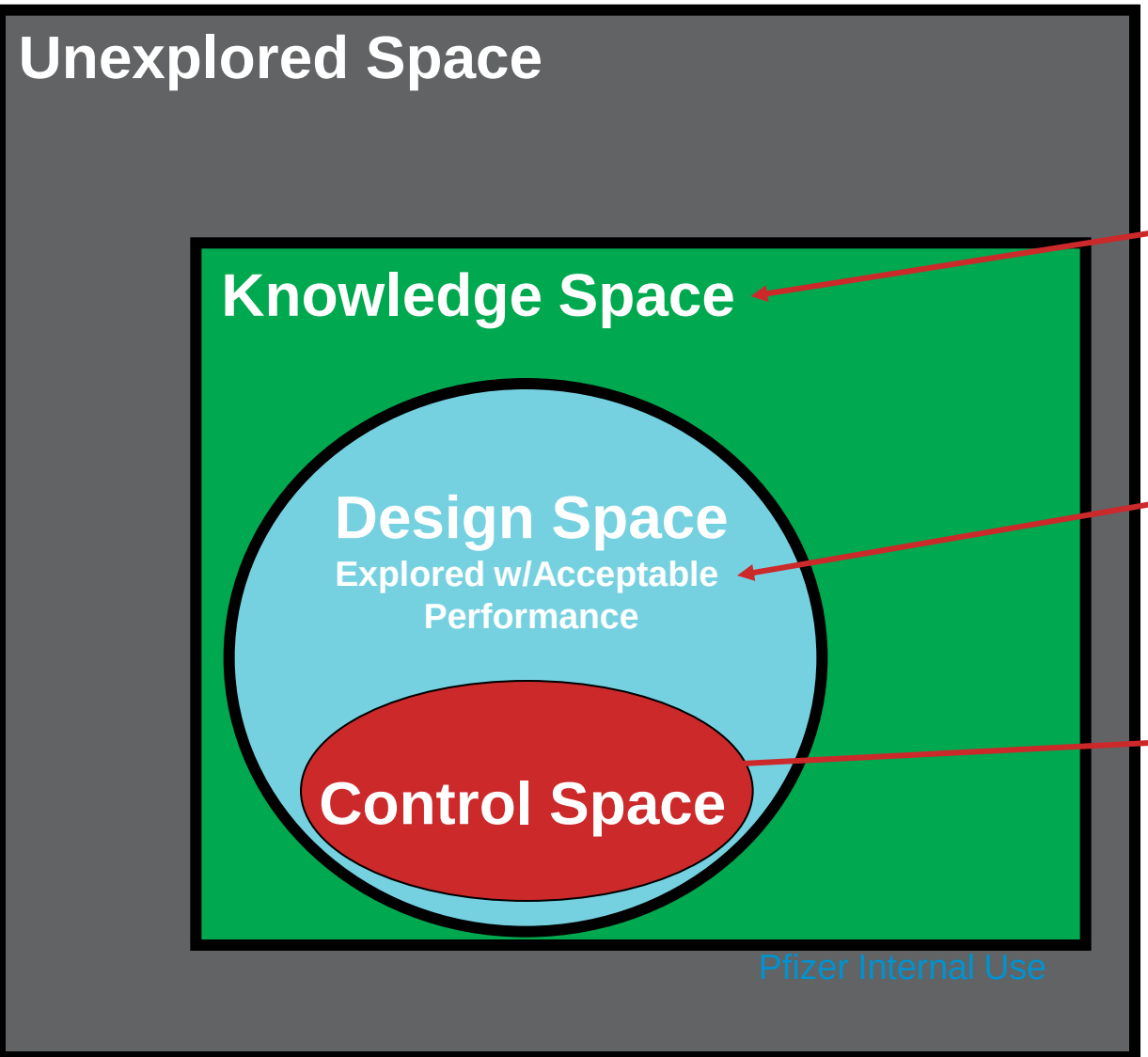
Simplified Description of Various "Spaces"



- Traditional DoE
- Mfg. Experience
- Process Understanding
- Multi-Product Precedent
- Modeling

PAR
Proven Acceptable Range

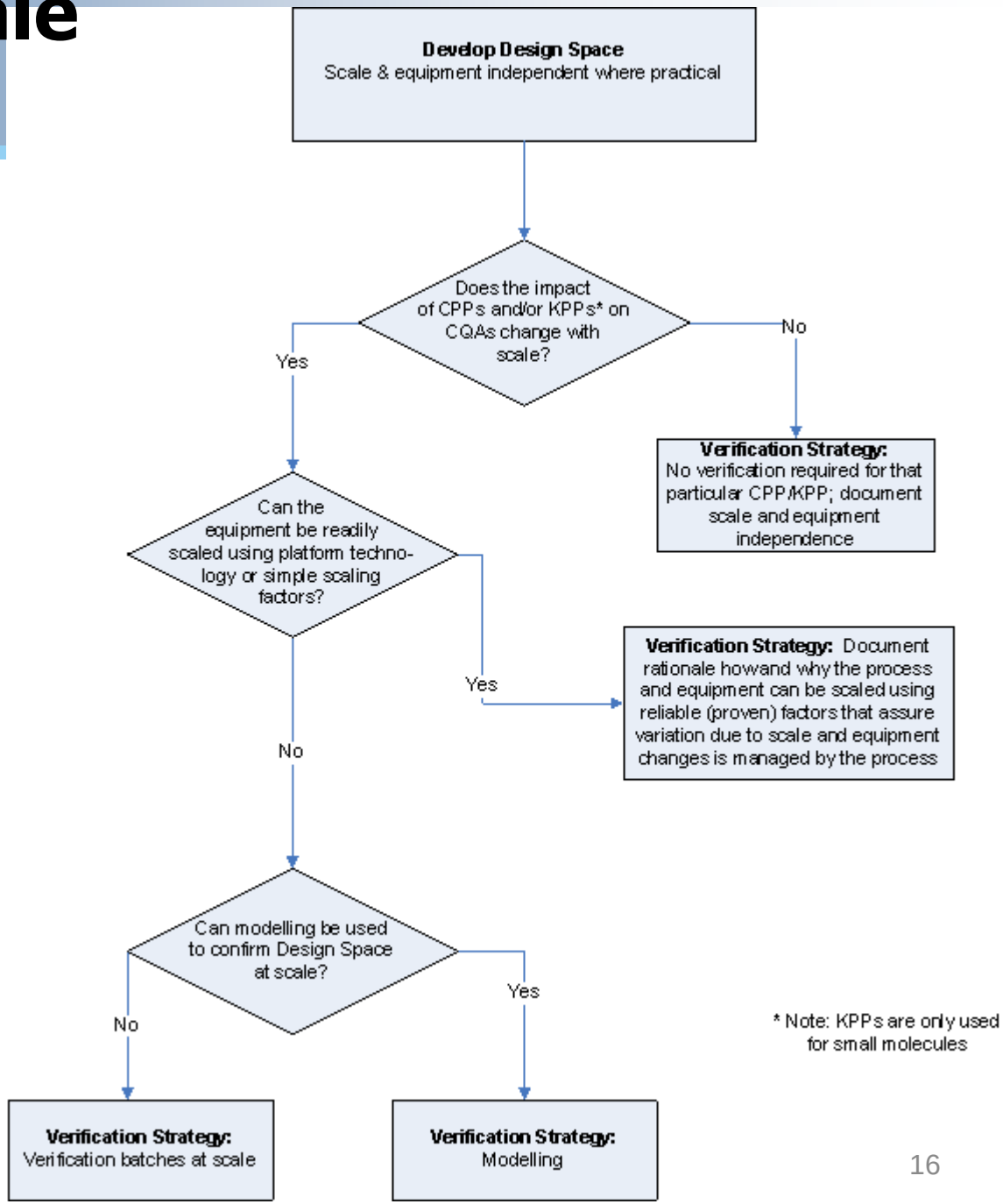
NOR
Normal Operating Range

Determining Scale Dependence

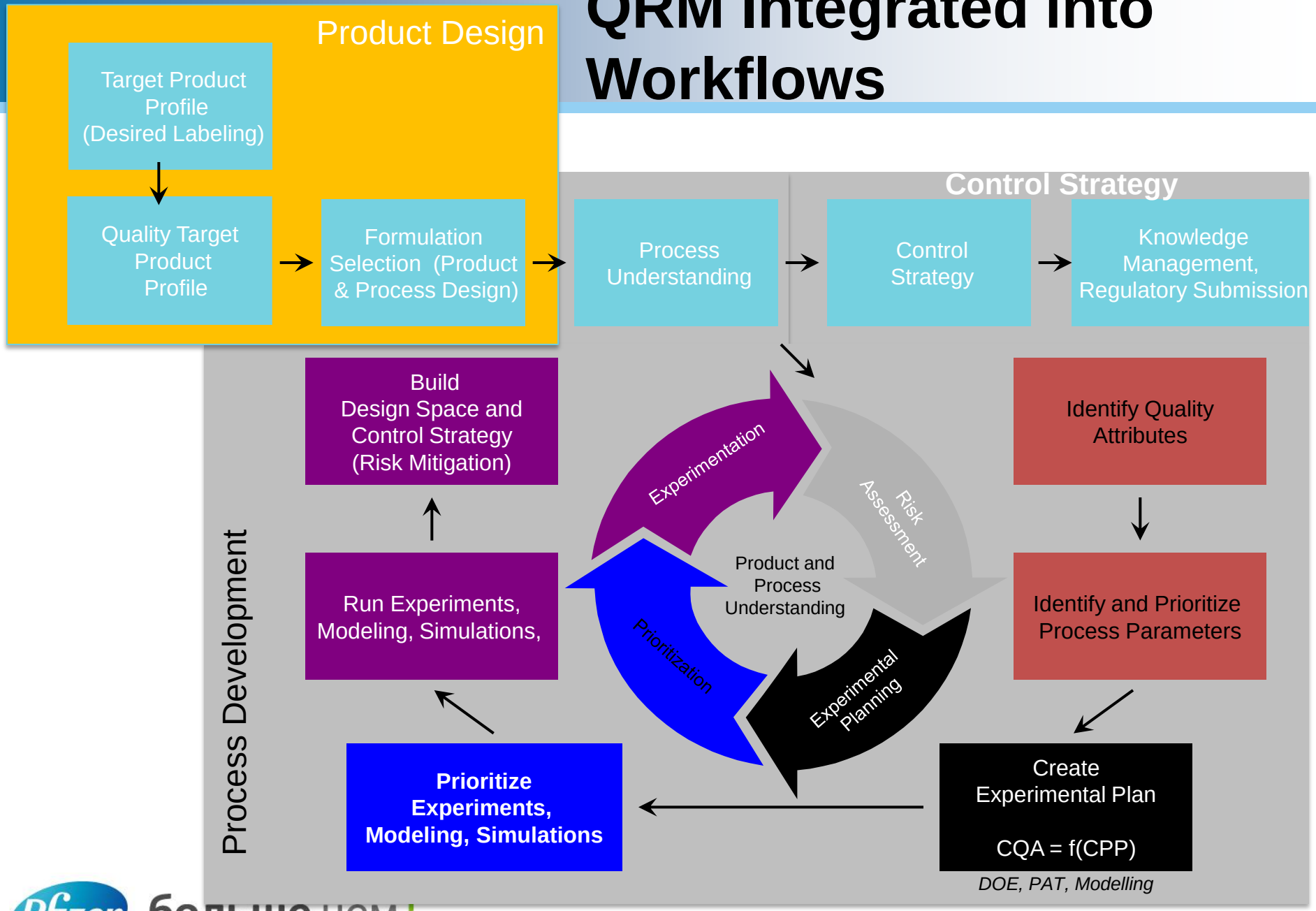
Flow diagram assesses scale sensitivity and identifies approaches to verify design Space

Teams should think about this during development experimental planning:

- Scale-dependant vs independent Process Parameters
- Consider when it's appropriate to include Process Parameters in small scale experiements



QRM Integrated into Workflows



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What is a Control Strategy

- **ICH Q10 definition:**
-
- "A planned **set of controls**, derived from current product and process understanding that **ensures process performance and product quality**. The controls can include **parameters** and **attributes** related to drug substance and drug product **materials** and **components**, **facility** and **equipment** operating conditions, **in-process controls**, finished product **specifications**, and the associated **methods** and frequency of **monitoring and control**."

Risk Mitigation Table

Risk Category (Line)	Risk Description	L/M/H	Impact (1-10, 10 being most significant	Risk Flag (Critical/ Routine/ Minor)	Risk Mitigation Plan	Timeline
Drug Product	If GI toleration is drug related then it is unlikely that the formulation will provide the fix.	H	10	Critical	*Additional mechanistic studies required to understand the root cause of the GI toleration. Reformulation could impact PK properties. Additional clinical studies required in parallel.*	*N/A*
Drug Product	If formulation excipients (e.g. SLS) are contributing to GI toleration issue then tablet must be reformulated while achieving sufficient drug exposure.	M	8	Routine	*Need solubilization technologies; however have limited approaches for acidic compounds such as solid dispersion or lipid-based formulation. Note this may require alternate drug substance form (e.g. Free Acid).*	*9-15 mon*
Drug Product	Need to optimize level of sodium lauryl sulfate to keep below daily allowable limit or possibly below IIG level without compromising API solubilization and Bioperformance.	M	5	Routine	*Optimize sodium lauryl sulfate level in the tablet while evaluating impact on the tablet dissolution and in-vivo PK.*	*6-12 mon*
Drug Product	Potential for the therapeutic dose to be in the range of 500 mg/day or higher. As the dose exceeds 250 mg/day or higher non-conventional dosage forms such as sachet may need to be investigated.	M	5	Routine	Develop high drug load tablet or alternate drug product (e.g. sachet). Evaluate feasibility of dry and wet granulation to increase the drug load in DPDs new Continuous Portable Manufacturing Process.	6-12 mon

Control Strategy creates Standards and Standardization

Lower Risks, Costs & Higher Quality

- **Standards allow for efficiency gains in R&D by applying prior lessons learned**
- **Examples of Pharmaceutical standards include standard:**
  - Workflows
  - Models
  - Materials
  - Platform processing technologies
  - Equipment
  - Testing

Good Risk Management Practices

Risk management should:

- Create value – e.g., increase robustness
- Be an integral part of organizational processes
- Be part of decision making
- Explicitly address uncertainty
- Be systematic and structured
- Be transparent and inclusive
- Take into account human factors
- Be based on prior knowledge as well as current project knowledge
- Be capable of continual improvement

Summary

R&D Perspective

•Risk management is foundational to our product and process understanding & knowledge management systems

•Standards and standardization are key elements of efficient risk and knowledge management

•Knowledge Management systems which enable across product learnings and leveraging of prior knowledge provide major benefits in costs, quality, timing and risk management

Manufacturing Perspective

•Quality risk management is an enabler to transfer robust manufacturing processes

•Structured knowledge systems provides rapid application of process knowledge supporting investigations and process improvements over the lifecycle

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