STRATEGIES FOR SUCCESSFUL SCALE-UP USING QUALITY BY DESIGN

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AGENDA

- Background
  - ICH Guidelines
  - Terms and Definitions
- Supporting Information
  - ISPE publications
- Scale Up and Technology Transfer Process
- Examples
- Conclusions

The Guidelines: Q8, Q9, Q10 and Q11

- Introduced QbD and associated opportunities
- To be applied to new and existing products
- Generics
- Small and large molecules
- Drug product (Q8) and drug substance (Q11)

- Q8, Pharmaceutical Development
- Q9, Quality Risk Management
- Q10, Pharmaceutical Quality System
- Q11, Development and Manufacture of Drug Substances

www.ICH.org

What does Quality by Design involve?

- A focus on the patient
- A focus on the product
- A science- and risk-based approach, underpinned by a quality system
- Could be applied throughout the product lifecycle, from development to manufacturing
- Continual improvement

Some Terms and Definitions

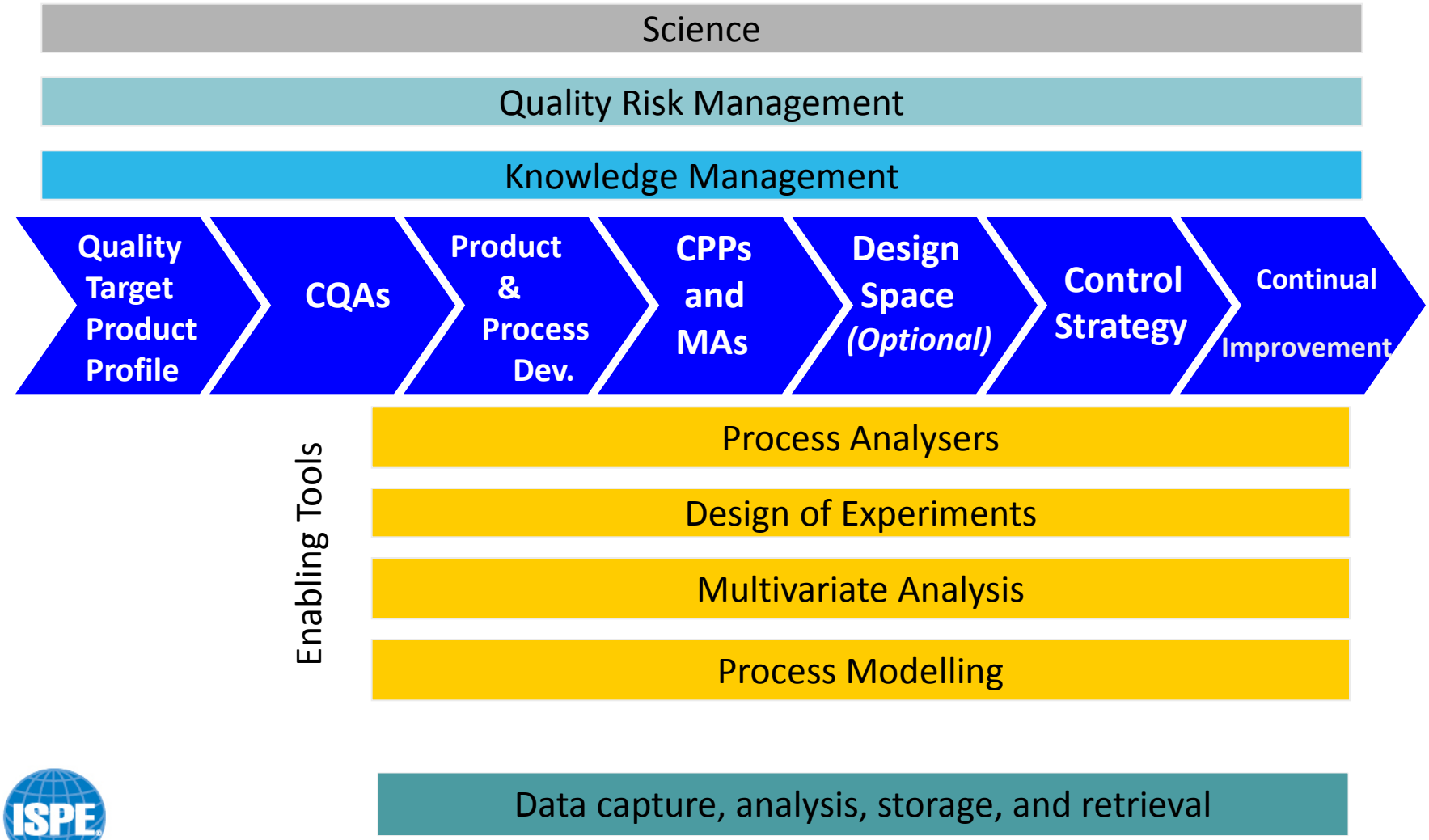
Quality by design
'A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.' ICH Q8R(2)

Quality Target Product Profile
'A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.' Q8(R2).

Critical Quality Attribute (CQA)
'A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.' ICH Q8(R2)

Critical Process Parameter (CPP)
'A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.' ICH Q8R(2)

QbD Roadmap



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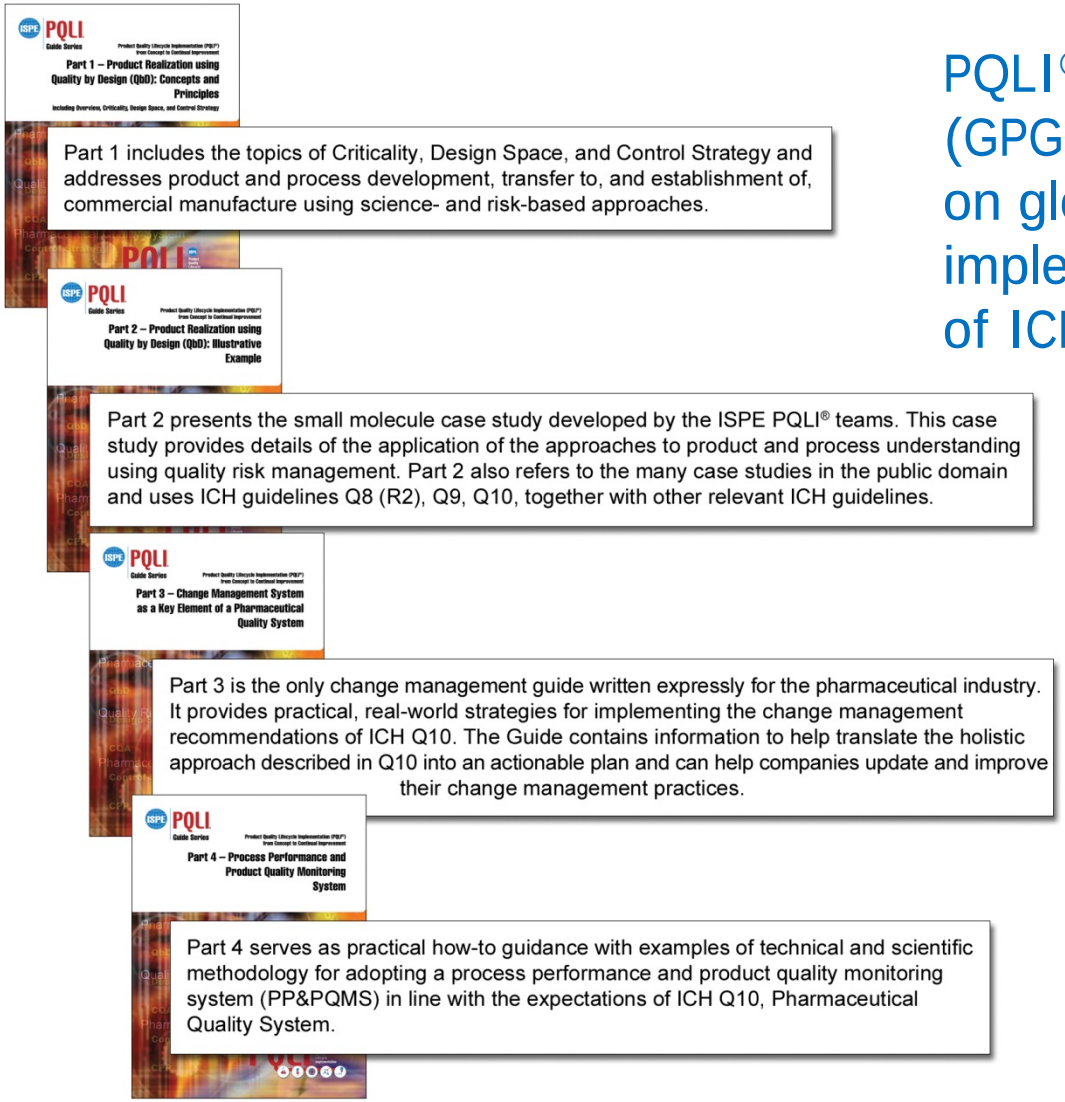
Good Practice Guides Parts 1, 2, 3 & 4



PQLI® Good Practice Guides (GPGs) provide information on global **solutions** to implementation challenges of ICH guidances

http://www.ispe.org/pqli-guides

PQLI® Parts 1 and 2 help with Scale Up and Technology Transfer for Product Realization using QbD Approach

Multifunctional Team
Scientists, Manufacturing, Engineering, Statistician, QA, etc

Scale of studies
Study design
Iteration
Use of PAT tools
Knowledge Management
Quality Risk Management

Product and Process Understanding
- Relevant to commercial manufacturing

Control Strategy

Objectives
- QTPP
  - CQAs
- Business

Scale Up and Technology Transfer Facilitated

ISPE Technology Transfer Scope

Applies to many types of scale up and technology transfer, e.g.

Drug Substance
Analytical
Drug Product

- Laboratory to laboratory scale
- Laboratory to development/pilot scale
- Development to clinical manufacturing
- Development to commercial manufacturing
- Commercial manufacturing to commercial manufacturing

ISPE Good Practice Guide, Technology Transfer revision due 2014

ISPE Technology Transfer Project Phases

- Form Technology Transfer(TT) Team & develop Charter
- Consolidate Knowledge for Transfer and agree high level TT Proposal
- Identify Risks, Conduct Risk Assessments, and develop TT plan
- Technology Transfer execution
- Process/procedure qualification
- Finalise Transfer and perform review

ISPE Good Practice Guide: Technology Transfer (Second Edition) – anticipated publication Q2 2014.

Technology Transfer Success Criteria

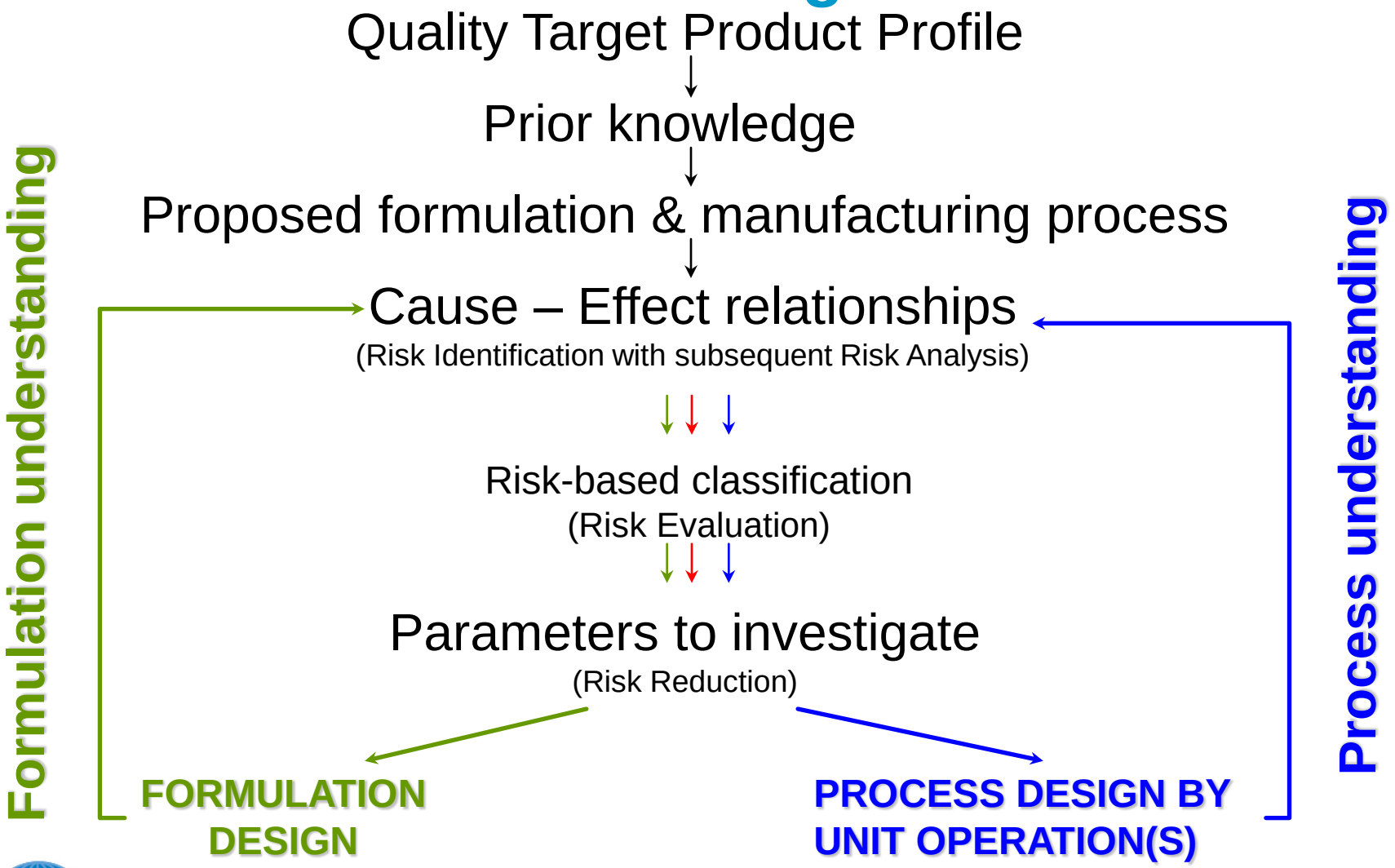
Depends on company policy, business situation and type of TT

Examples:

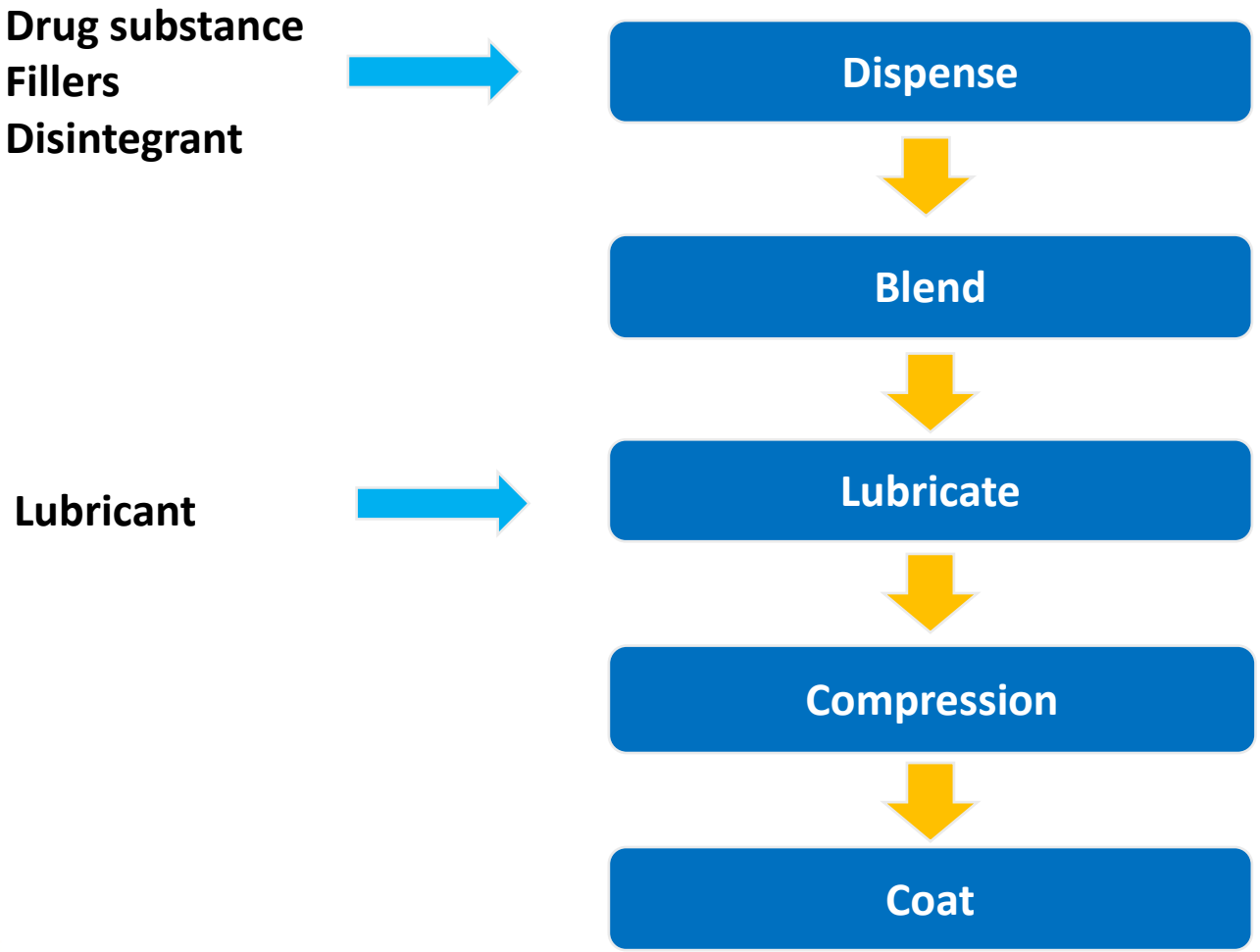
- Process/analytical procedure meets acceptance criteria
- Process validation/process performance qualification, stage 2 achieved
- Pre-agreed process capability metrics achieved

Ultimate measure of Scale Up success

Iterative Approach and Link to QRM Process - Drug Product



PaQLInol Tablet Manufacturing Process



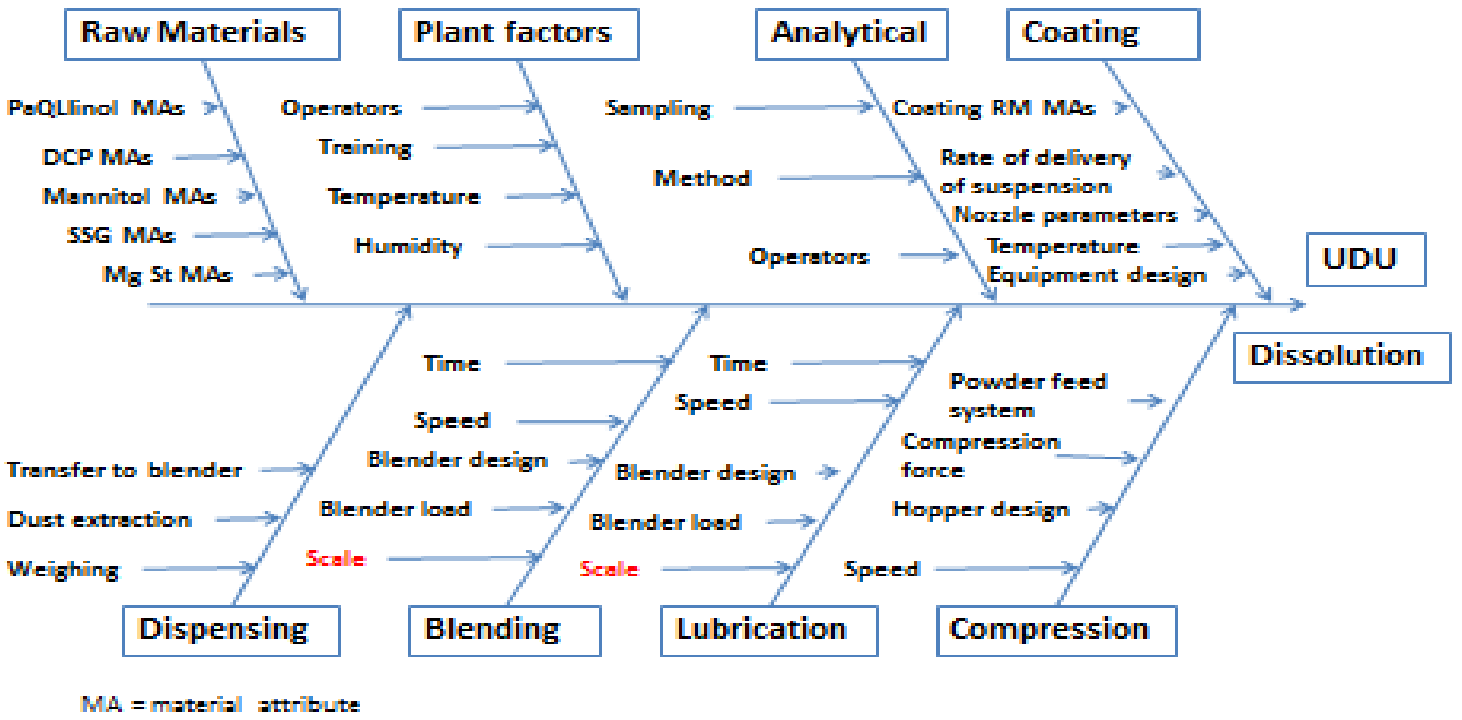
Quality Risk Management Process

- Risk Assessment
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation
- Multi-functional team
  - Scale up and manufacturing factors considered
- When using a formal process
  - Use a facilitator
  - Set scope
  - Manage carefully

Risk Identification

Cause and Effect Diagram for UDU and Dissolution for All Tablet Unit Operations

Use multi-disciplinary team in QRM exercise



MA = material attribute

Summary Output from Risk Evaluation using FMECA as a Matrix

Before Process Development Studies

	Dissolution	UDU	Appearance
PaQLInol particle size	H	M	L
Mg St material attributes	H	L	M
DCP MAs	M	L	L
Mannitol MAs	M	L	L
SSG MAs	L	L	L
Blending time	L	M	L
Lubrication time	H	M	L
Compression force	H	L	L
Blender design	L	M	L
Blender speed	L	M	L
Blender loading order	L	L	L
Blender load factor	L	M	L
Blender Scale	M	M	L

Initial Approach to Understanding the Process

- Study impact of
  - PaQLInol particle size, — Scale independent
  - Magnesium stearate surface area, — Scale independent
  - Blending time, — Scale dependent
  - Lubrication time, — Scale dependent
  - Compression force — Equipment dependent
- on CQAs Dissolution and UDU
- Review results and conduct a risk assessment exercise to establish if there has been any risk reduction

Consider UDU from Blending Unit Operation

- From FMECA
  - 7 factors of medium risk to study, 6 scale dependent

Options

Conduct multiple studies to develop process understanding - algorithm

Control Strategy 1
Based on controlling and understanding parameters and raw material attributes

Develop an in-line method (NIR) to measure blend uniformity

Control Strategy 2
Based on measuring attribute of blend

Manufacturing and Engineering have input to decision

Conclusions

- Enhanced, QbD approach can bring substantial benefits e.g.
  - Build scale factors into development studies
- Systematic approach keeps development program focused
- Involving Manufacturing, Engineering, QC, QA etc. in QRM exercises facilitates:
  - Design of studies
  - Decision-making
  - Preparation for scale up and commercial manufacture

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Many hands make light work!!

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PQLI® ISPE Product Quality Lifecycle Implementation