Design Space and Control Strategy

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SAQ
Olten 2006

Outline

- ICH Q8, Q9 and Q10 – The Vision of the desired state
- Q8 is a Door Opener for
  - Describing Quality by Design
  - Including more Science and Risk Management
  - Including PAT
  - Include Design Space
- Introduces the concept of Design Space
- Describes how to define what is critical
- Redefines what is a Change
- Quality Risk Management supports the Control Strategy
- Summary

Global Challenges

- Rising Global Regulatory Bar
- Consent decrees and enormous fines from manufacturing compliance deficiencies
- Higher safety hurdles for marketing approval
- Challenge of Sustaining Product Pipeline & Flow
- Biotech contribution less than expected
- Government price control
- Challenge of Earning Stakeholders Trust

Fritz Erni

Ref: Fred Hassan – CEO Schering-Plough

FDA's 21st Century Quality Initiative

- Goals

1. Encourage the early adoption of new technological advances by the industry

2. Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance

3. Encourage implementation of risk-based approaches that focus both industry and FDA attention on critical areas

•**Woodcock, FDA**

The Paradigm Change

From
'blind compliance'
to
'science and risk based compliance'

Ajaz Hussain, FDA

ICH agreed Desired State

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to effect Continuous Improvement and Continuous "real time" assurance of quality

GMP and Regulatory Actions

FDA Pharmaceutical cGMP for the 21st Century – a Risk based Approach

FDA PAT guideline

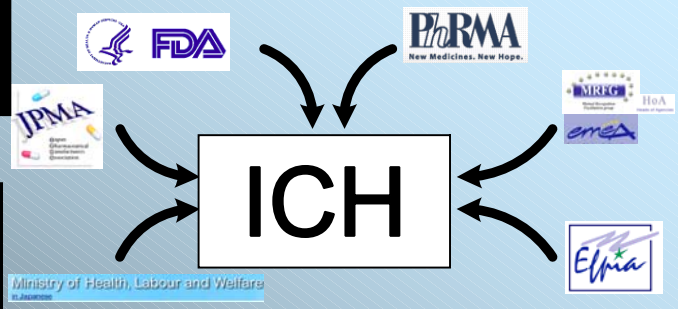
2004
2005
2006

FDA : Innovation and Continuous Improvement in Pharmaceutical Manufacturing

FDA Draft Quality Systems

Q8
Pharmaceutical Development

Q10
Pharmaceutical Quality System



Q9
Risk Management

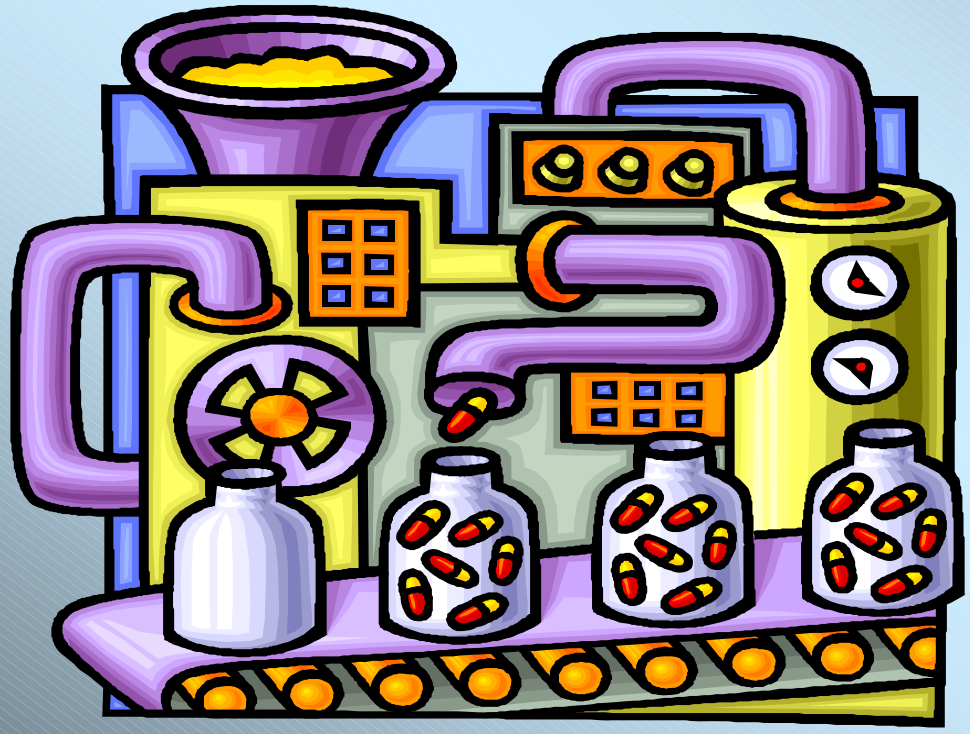
Update
Q6A/B ?

Process Analytical Technology : PAT

- FDA's Vision :
  - Paradigm Change:

    Quality by design replaces Testing to Document Quality
  - Product and Process specifications based on mechanistic understanding of how factors affect product performance
  - Process understanding leading to
    - Real Time Quality assurance
    - Continous Improvement
  - Regulatory policies tailored to science
  - Risk based approaches

The role of Process Understanding



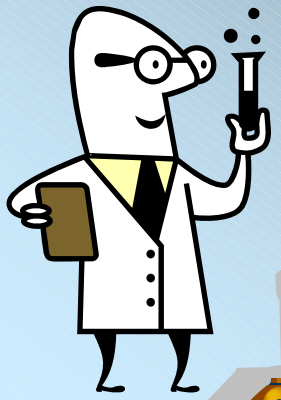
Process Understanding

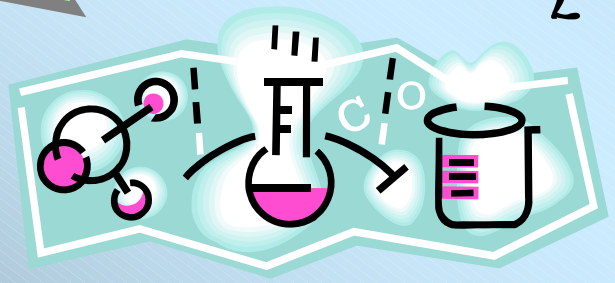
- Pharma

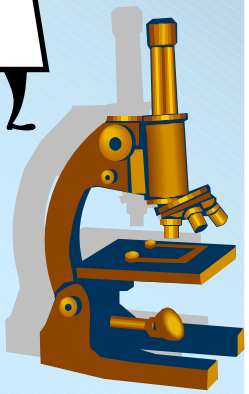
- Air Plane

Challenges to ‘Understanding’

- Understanding involves Measurements







Challenges to Analytical Science

The need for increased

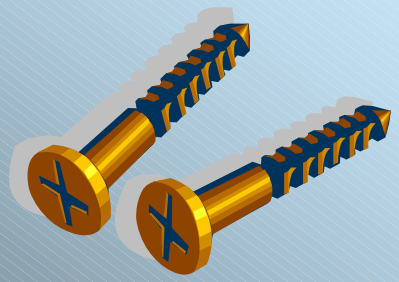
Process understanding is

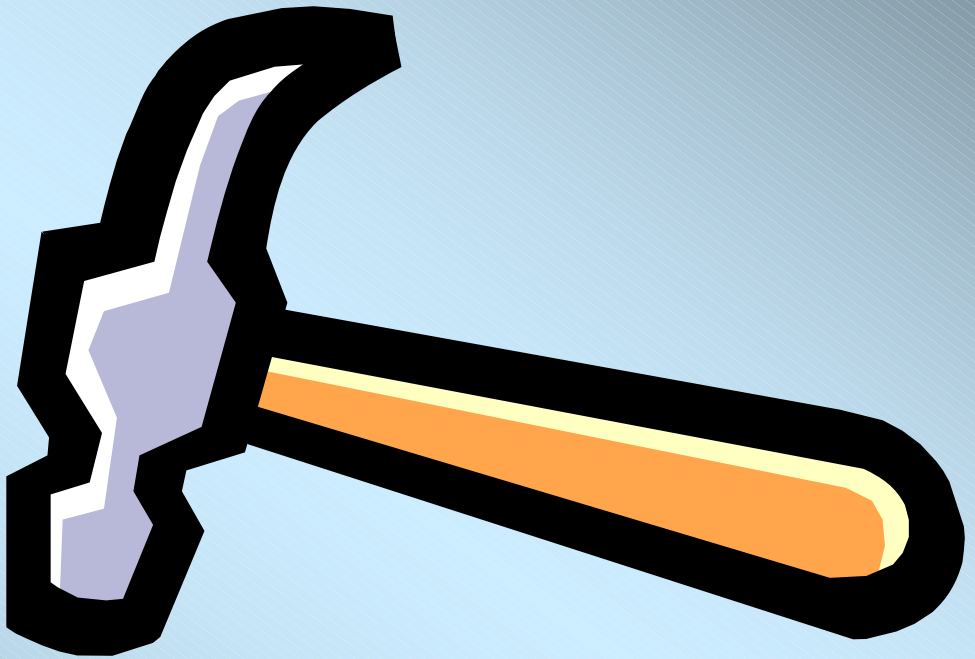
a massive Boost for

Analytical Science

Challenges to Analytical Science

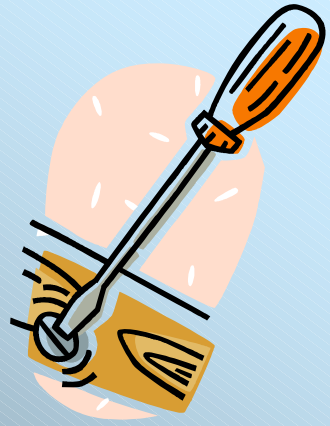
adequate Tools?

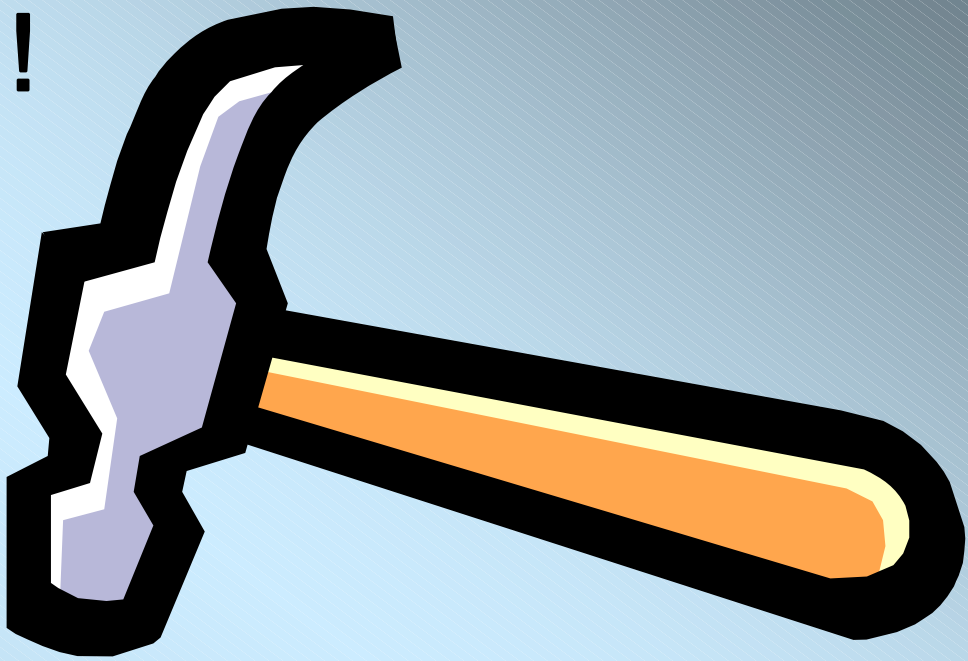


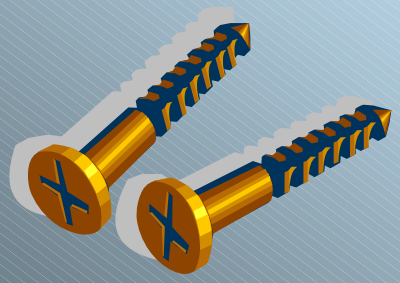


Challenges to Analytical Science

adequate Tools !



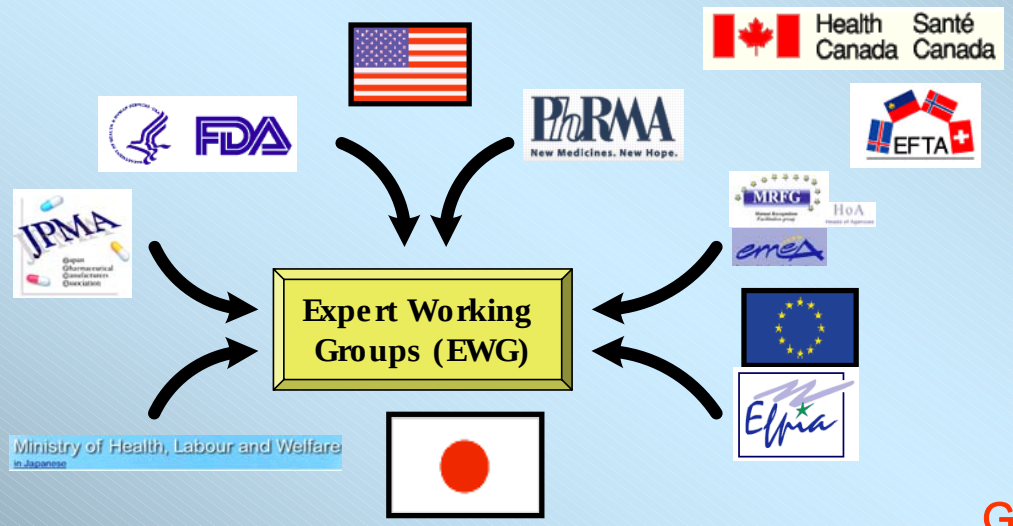




Challenges to Analytical Science

We need the adequate Tools

Global Harmonisation (ICH+GCG)



ICH

Global Cooperation Group

WHO

APEC : Asia Pacific Economic Cooperation

ASEAN : Assoc. South East Asian Nations

GCC : Gulf Cooperation Council

PANDRH : Pan American Network for Drug Reg. Harm.

SADC : South African Dev. Community

What is Q8 be!

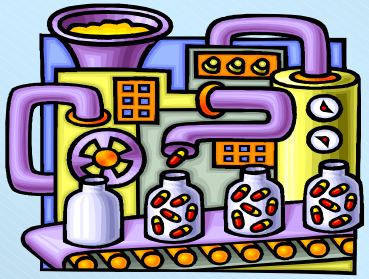
- Guideline for the description what is in P2
- Describes the minimal Standard for P2
- Opens door to get closer to the

  ‘Desired State’

  - Science based
  - Includes Risk Management
  - Continuous improvement
  - Real Time Release

ICH Q8

Door opener for
Quality by Design



What is Quality by Design

Elements of a QbD

- Systematic Development Approach
- Formulation Understanding
- Process Understanding
- Packaging Understanding
- Application of Quality Risk Management
- Advanced Control Strategy

Quality by Design

Conventional PD	Quality by Design(ideal)
Mainly empirical approach	A systematic approach
Quality assured by end-product testing and inspection	Quality assured by well understood product and process, moving controls upstream without relying on end-product testing as much as possible
Process is fixed, disallowing changes	Flexible process within design space, allowing continuous improvement
Focus on process reproducibility – often avoiding or ignoring variability	Focus on formulation and process robustness – understanding and controlling variability
Limited and simple IPC	Extended PAT tools replacing the need for end product testing

P2 Content per CTD-Q

1. Drug substance
   - Key physicochemical characteristics
   - Compatibility
2. Excipients
3. Drug product
   - Rationale for type of product
   - Formulation development
   - Overages
   - Physicochemical and biological properties
   - Performance testing
4. Manufacturing Development
5. Container closure system (and delivery devices)
6. Microbiological attributes
7. Compatibility

Where to put information in on

- Quality by design
- Science
- Risk Management
- Continous improvement
- Real Time Release

When to update the document

Where do we stand?

- Q8 Step 4 signed by 6 ICH partners and observers

- Confirmed main Strategic issues

- Clarifying ‘baseline’ and ‘optional’ expectations

- Outlined areas of potential regulatory flexibility that could be expected when presenting ‘optional’ information

Q8 – General Concepts
QbD and Risk Management

- The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process.

Q8 – General Concepts
QbD and Risk Management

- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls.

Q8 – General Concepts

What is minimal requirement

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.

Q8 – General Concepts

What is critical?

Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

Q8 – General Concepts

Optional process understanding

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters.

Q8 – General Concepts
What we get in return

This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of post-approval submissions;
- real-time quality control, leading to a reduction of end-product release testing.

Possible Regulatory Flexibility

- Continuous Improvement
- Real time release
  - Reduced or elimination of routine end product testing
- Expanded design space
  - Independence on scale
  - Independent of equipment
  - Independent of site
  - Independent from drug substance manufacturing if within spec
- Process Validation
  - Process validation replaced by Concurrent Process Verification using validated methods (qualified controls)
- Stability Testing
  - Reduced confirmation stability studies for any changes within the design space
  - Reduced annual stability batches

Q8 – General Concepts
Review - Inspection

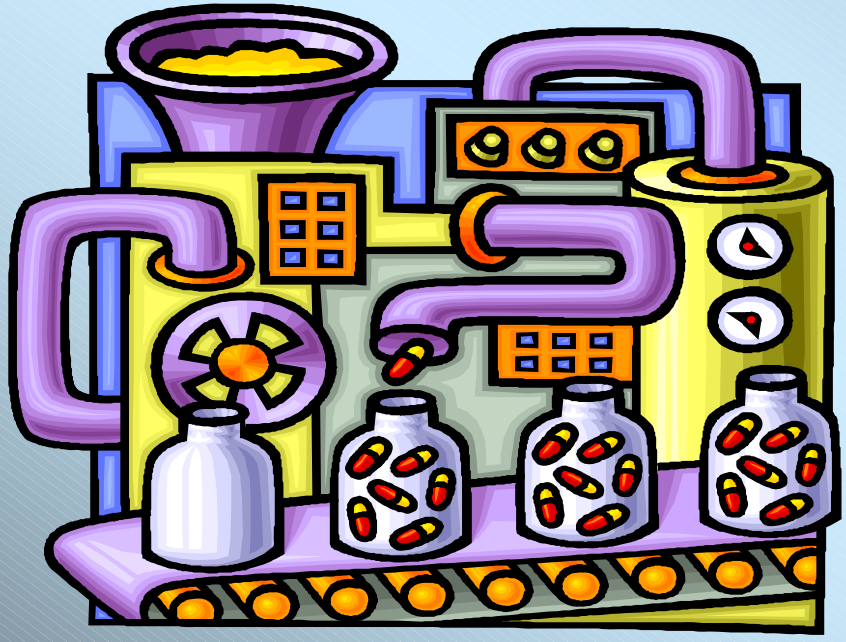
The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

Q8 – Strategic Questions : Submissions and Post Approvals

It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product

Process understanding

Key for making a good story!



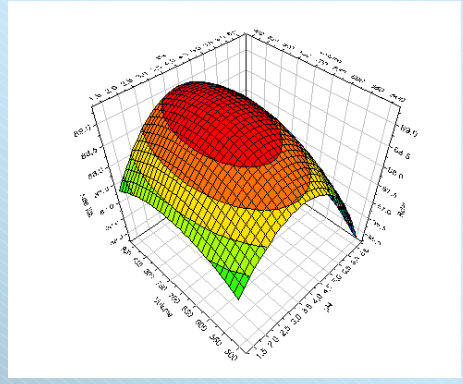
Q8 – Strategic Questions :

What is the Design Space?

Will be the Base for Continuous Improvement!

Design Space

- Is Key for claiming Process Understanding
- Process understanding is Key for Quality Risk Management
- QRM is the base for any Control Strategy



Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Q8 – Design Space :

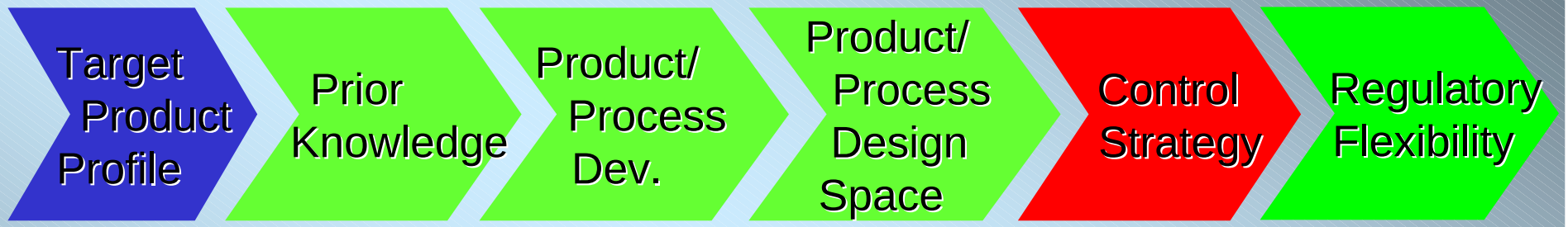
Redefines what is a Change?

Base for all Post Approval Changes

EFPIA PAT Topic Group

Chris Potter	AstraZeneca: Chairman
Rafael Beerbohm	Boehringer-Ingelheim
Alastair Coupe	Pfizer
Fritz Erni	Novartis
Gerd Fischer	Sanofi-Aventis
Staffan Folestad	AstraZeneca
Gordon Muirhead	GSK
Stephan Roenninger	F Hoffmann-La Roche
Alistair Swanson	Pfizer

An Industry View of QbD in Dossier: Key Scientific Elements and 'Flow'



Definition of **Product Intended Use** and pre-definition of **Quality** targets (wrt clinical relevance, efficacy and safety)

Summary of **Prior Scientific Knowledge** (drug substance, excipients; similar formulations and processes). **Initial Risk Assessment**

Overview of **Quality by Design** key actions and decisions taken to develop **New Scientific Knowledge**, e.g. DoE, PAT, **Risk Assessment** and **Risk Control**

Summary of **Scientific Understanding of Product and Process**. Justification and description of **Multi-dimensional Space that Assures Quality** (interrelation-ships and boundaries of **Clinical Relevance**).

Definition of **Control Strategy** based on Design Space leading to **Control of Quality** and **Quality Risk Mgmt.** (Process Robustness)

Proposal of **Regulatory Flexibility** based on Product and Process Scientific Knowledge and **Quality Risk Mgmt.** (Materials, Site, Scale etc)

Design Space (ICH Q8)

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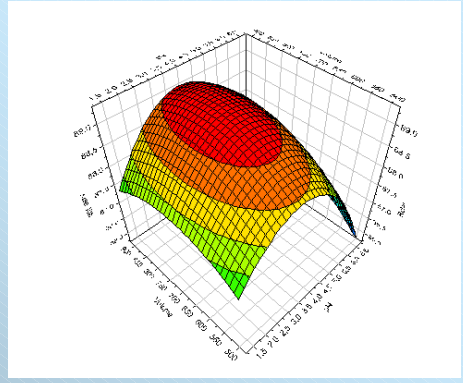
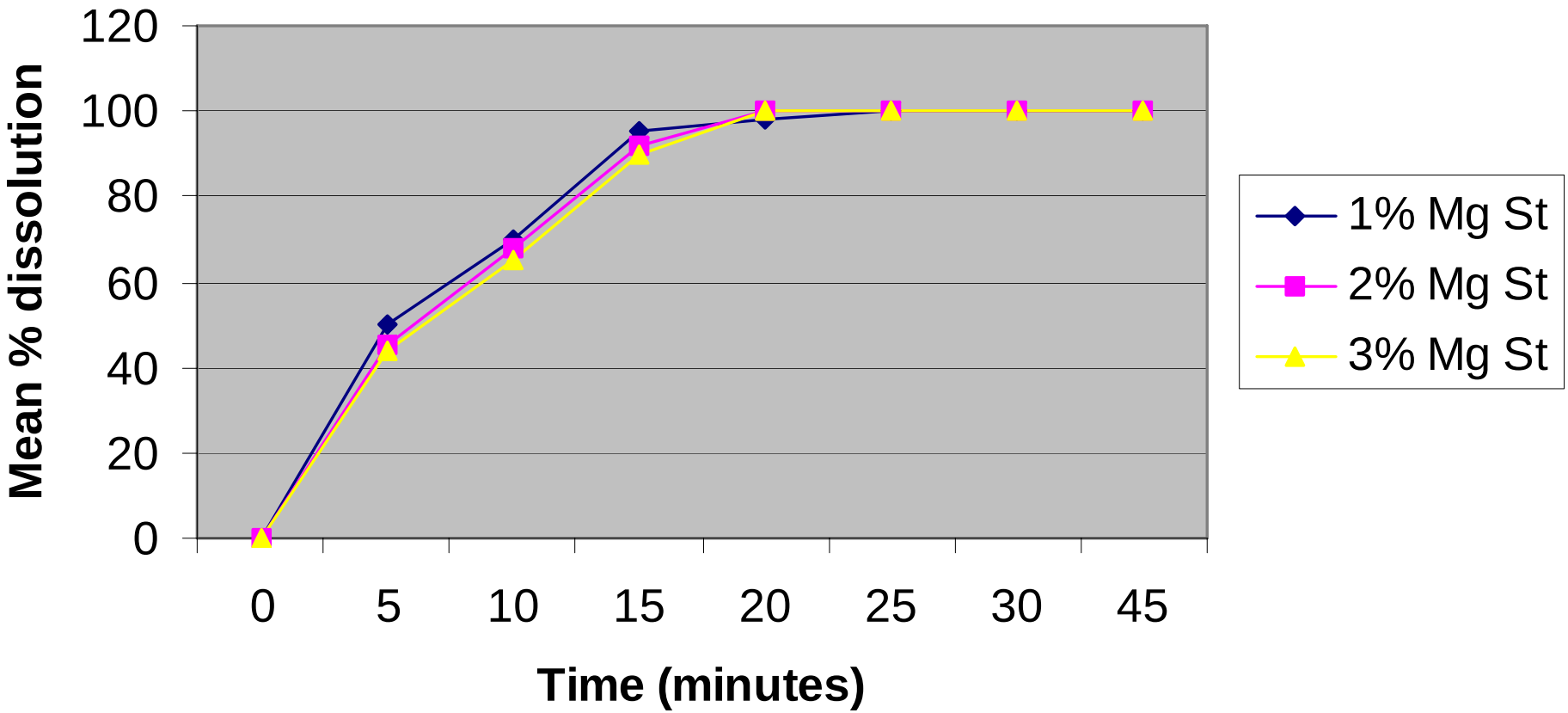
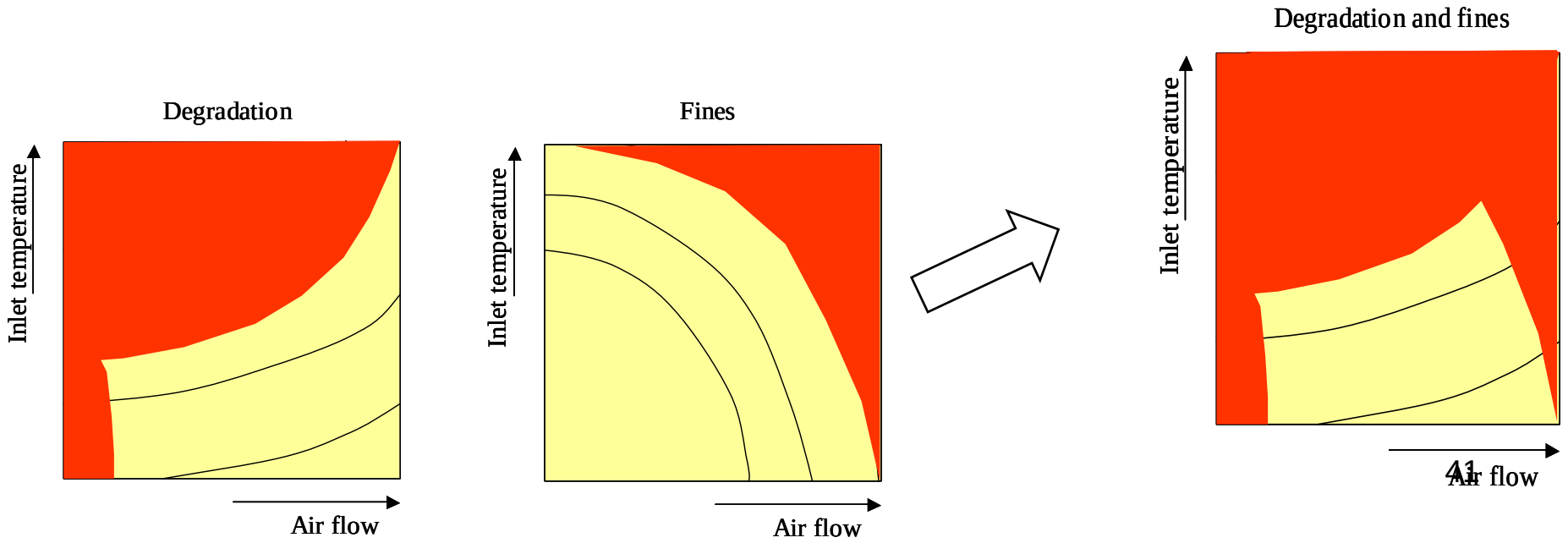


Dissolution profiles of examplain hydrochloride tablets - effect of lubrication level pH 6.8

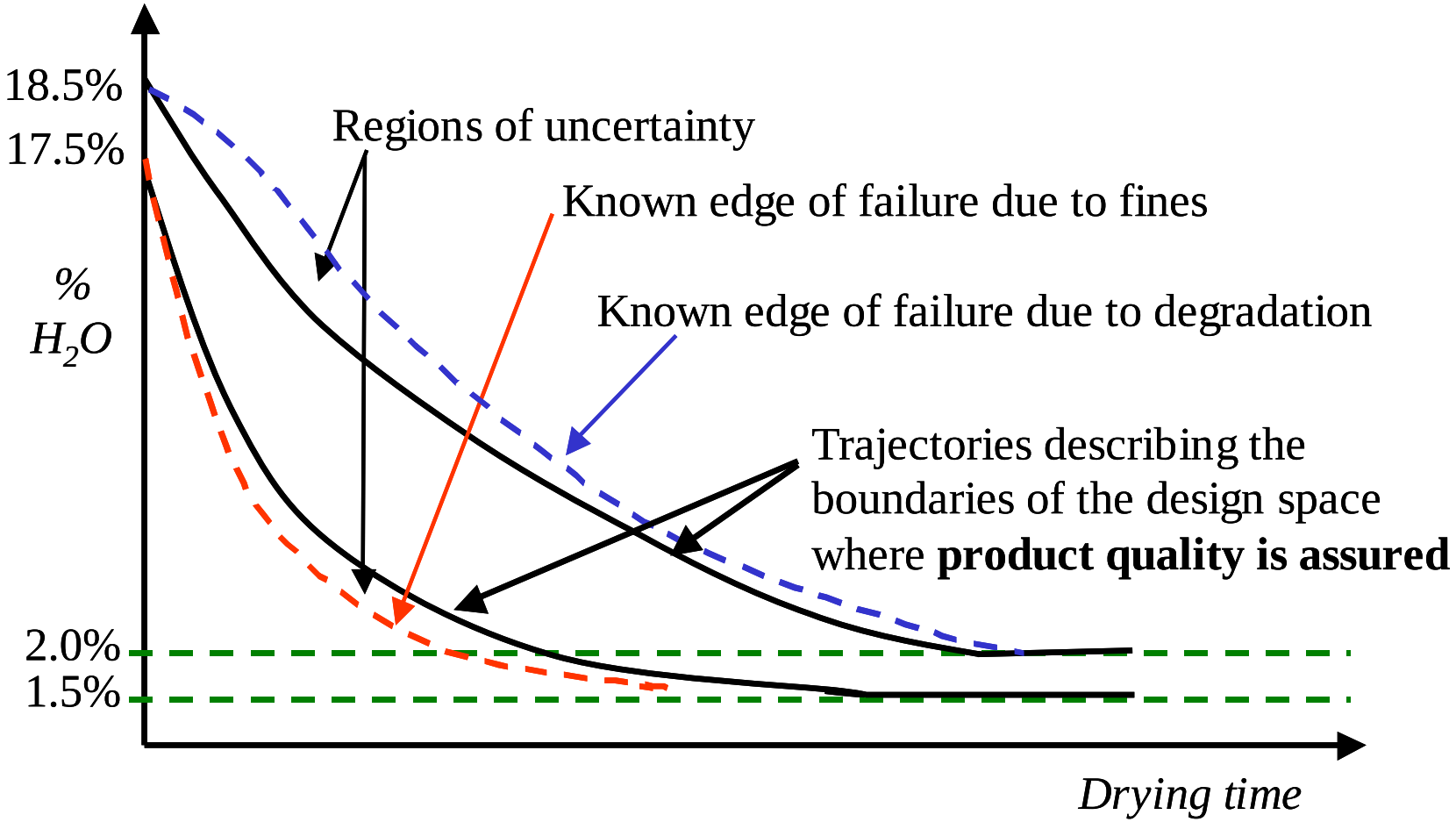


Design of Experiments (DoE)

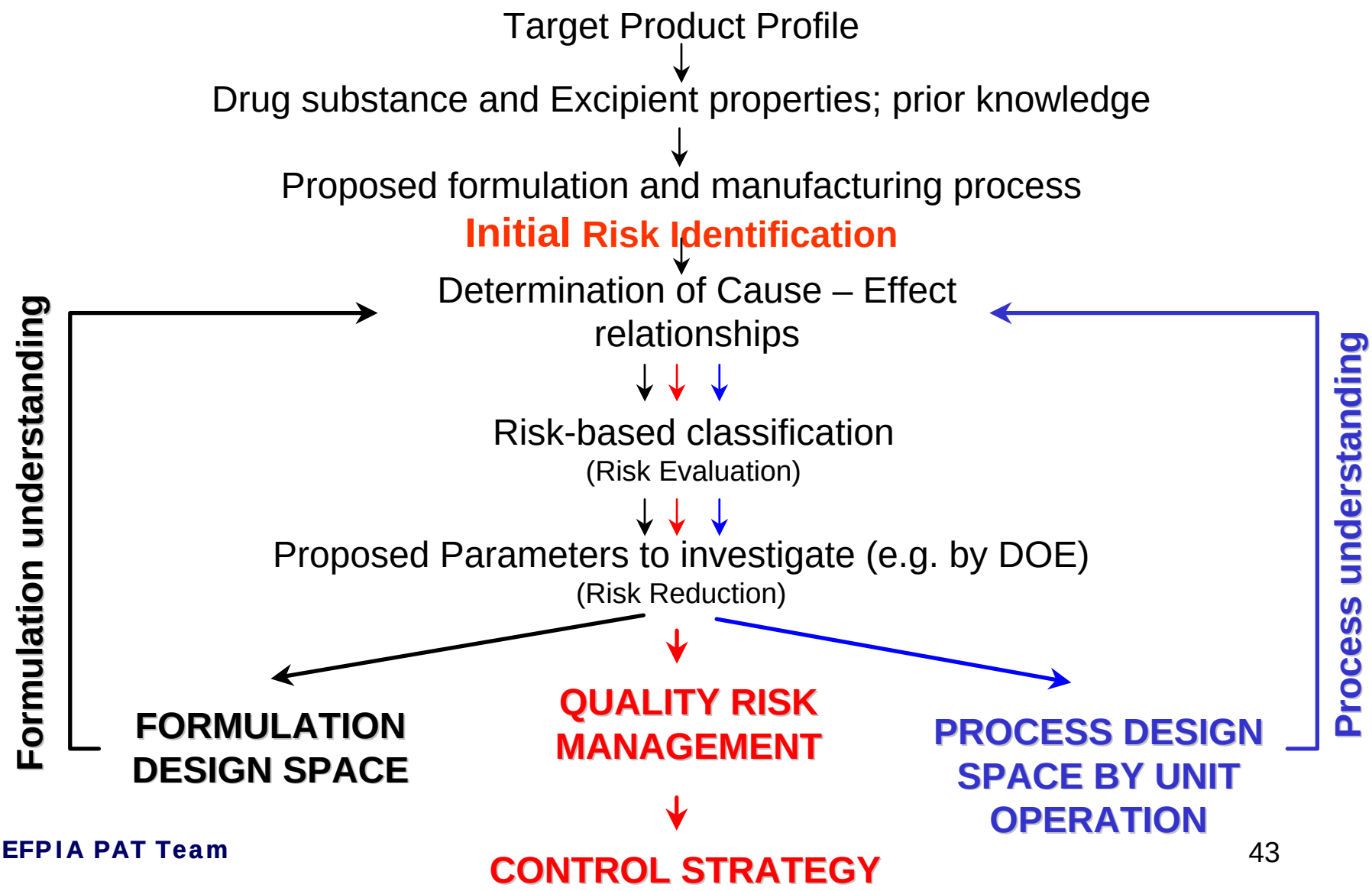
Effect of inlet temperature and air flow on degradation and generation of fines



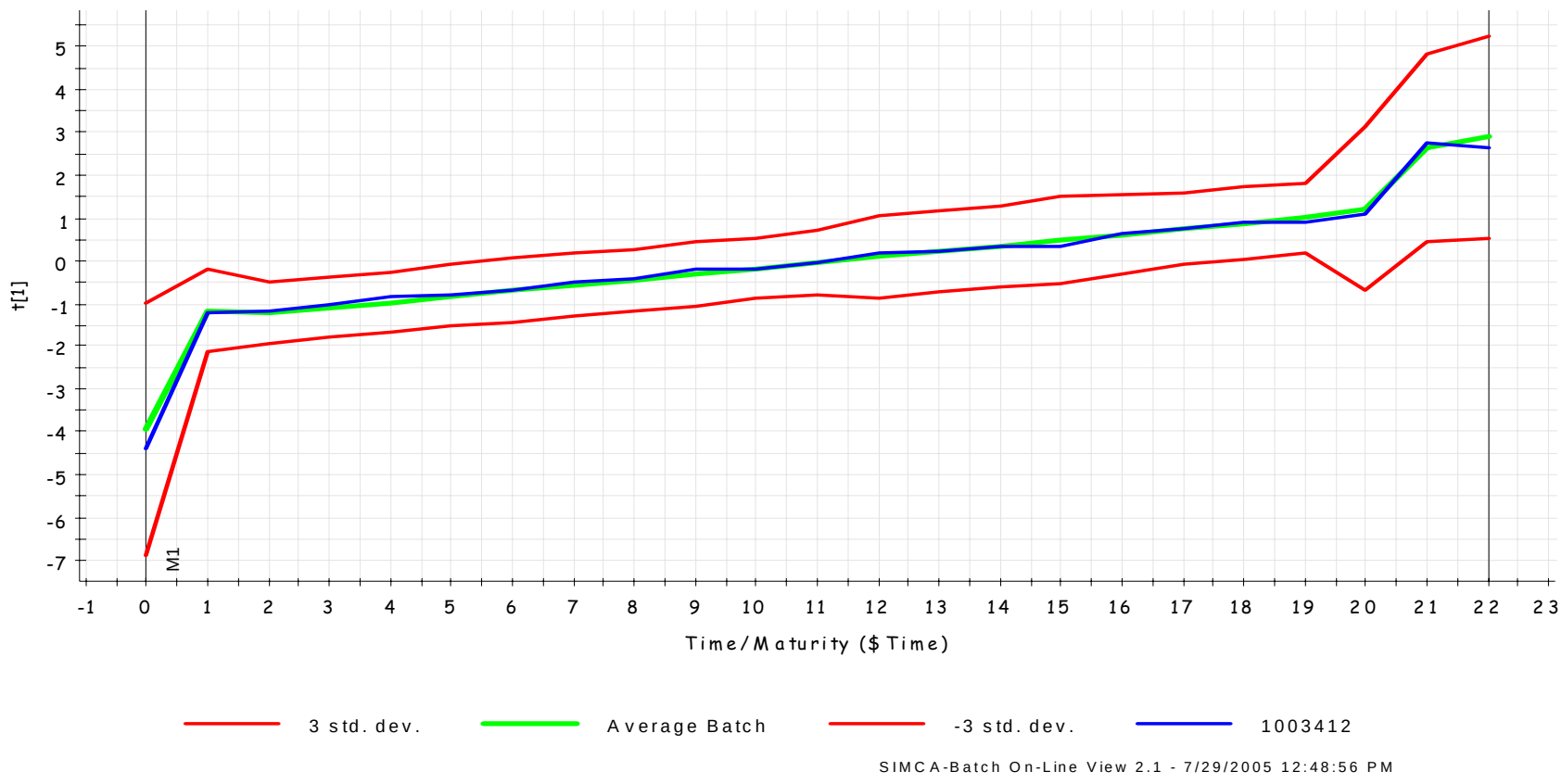
Examplain Design Space – Graphical Description



PAT Development Approach



Real-Time Monitoring



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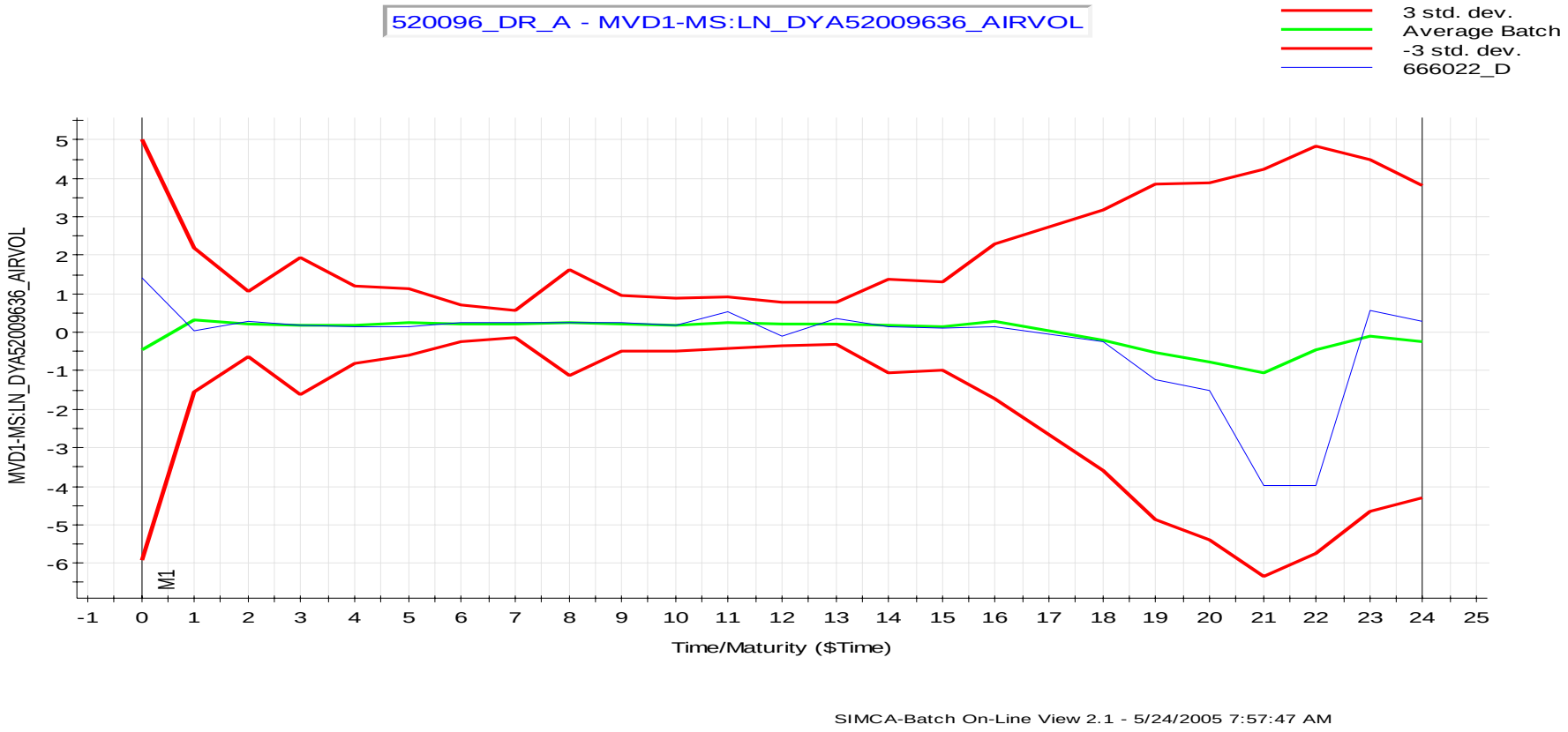
Plot For One Variable



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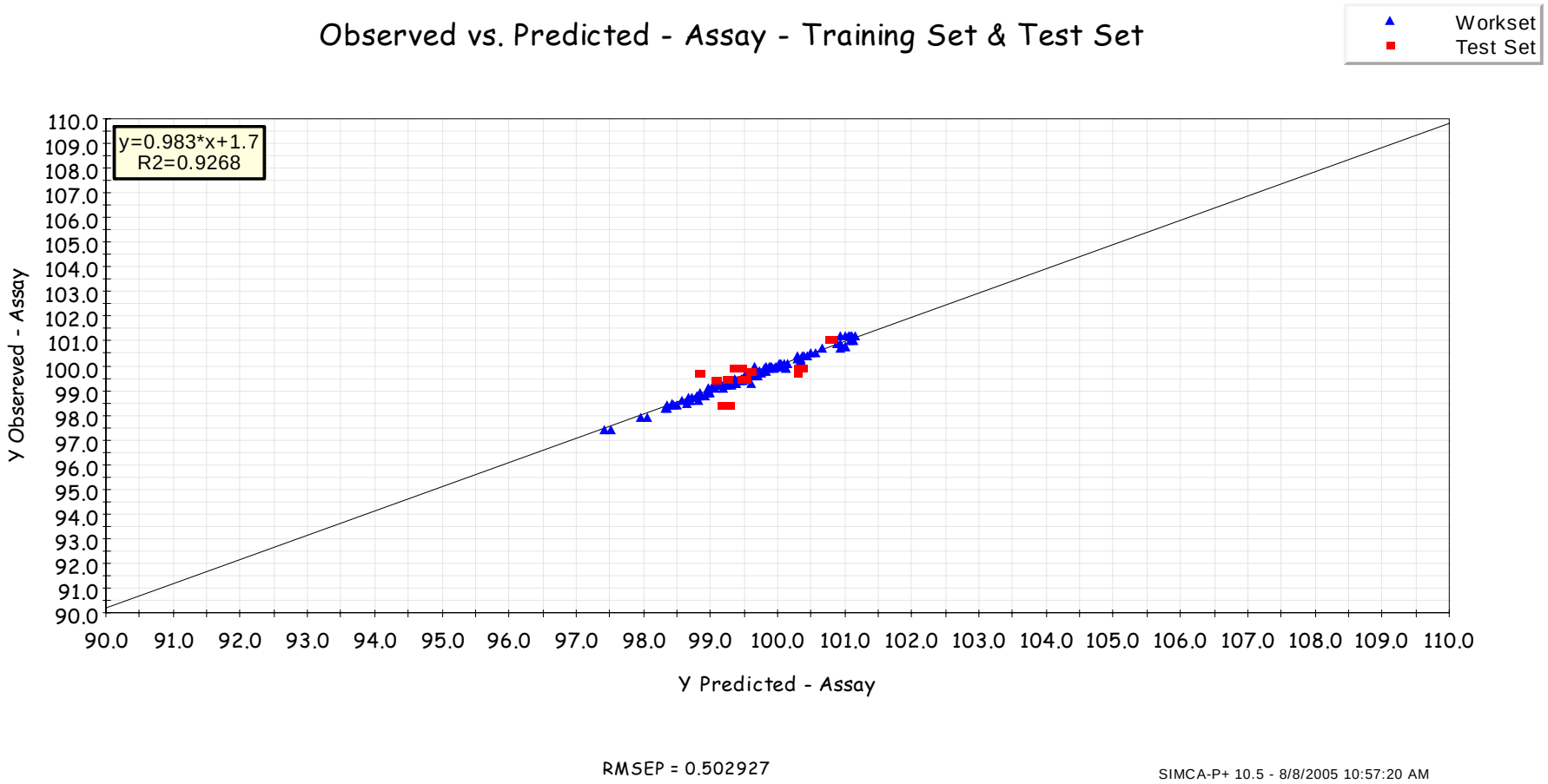
Assay – Training Set & Test Set



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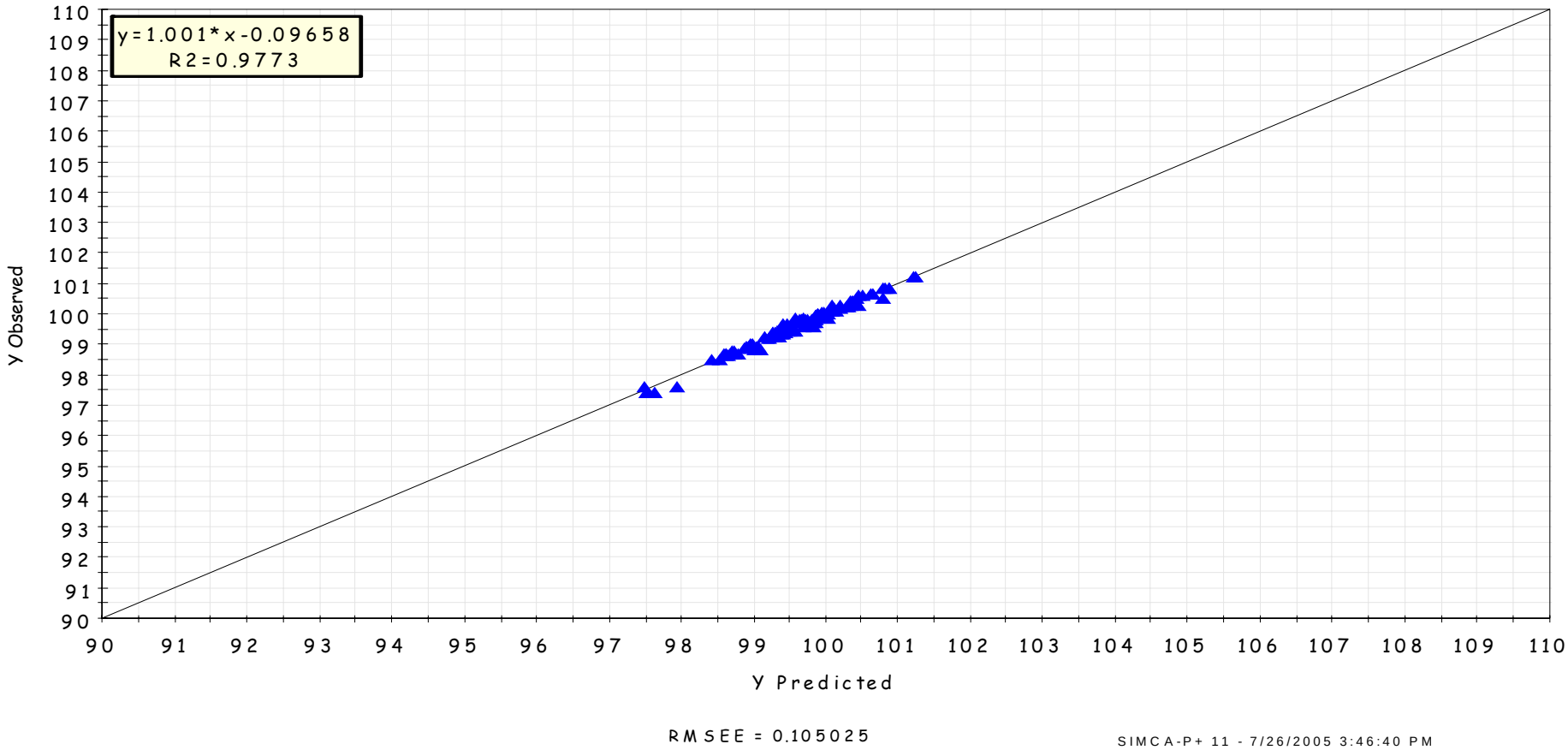
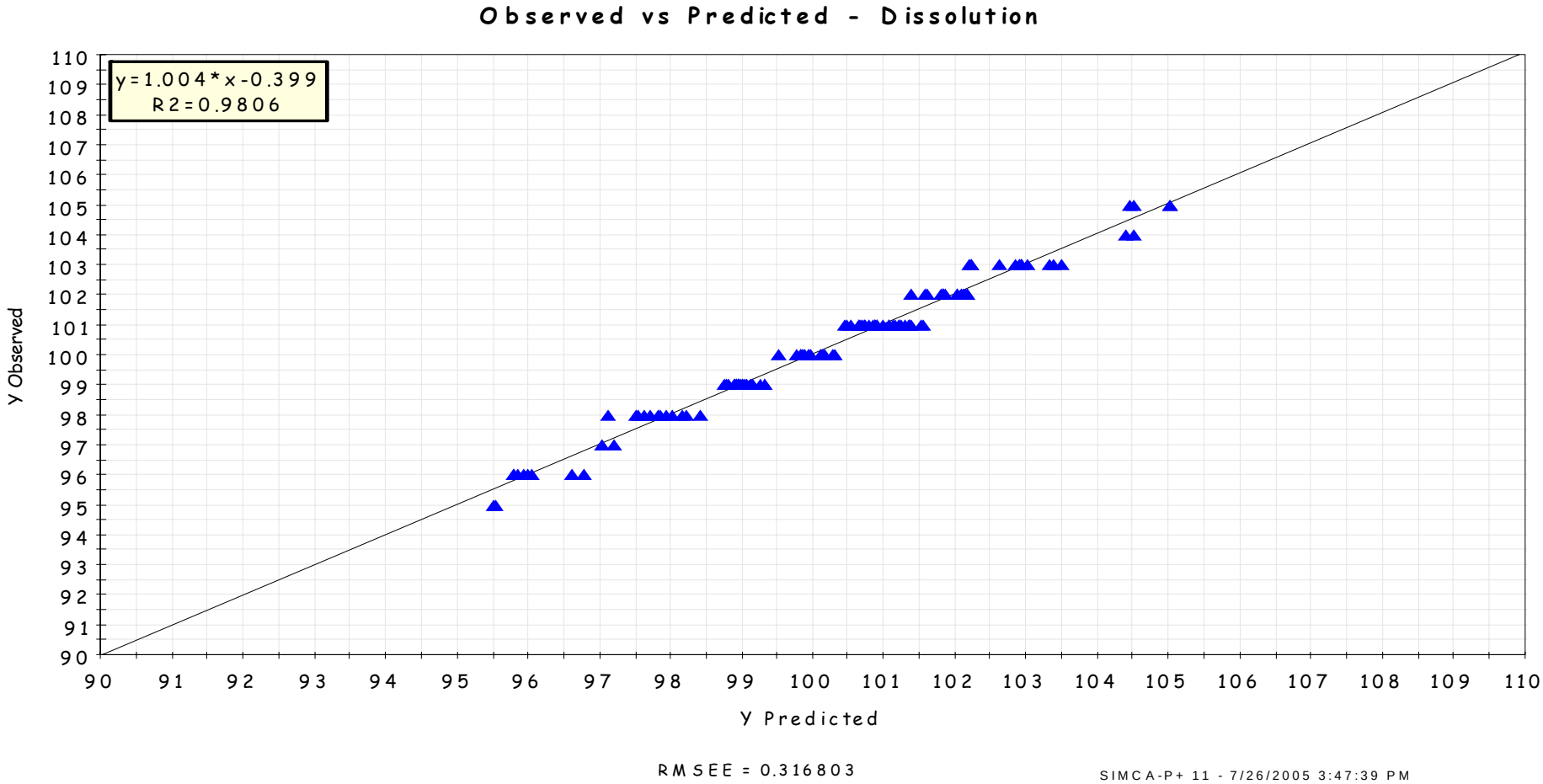
MVBA Results



MVBA Results



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ICH Q8 : Important points for Industry

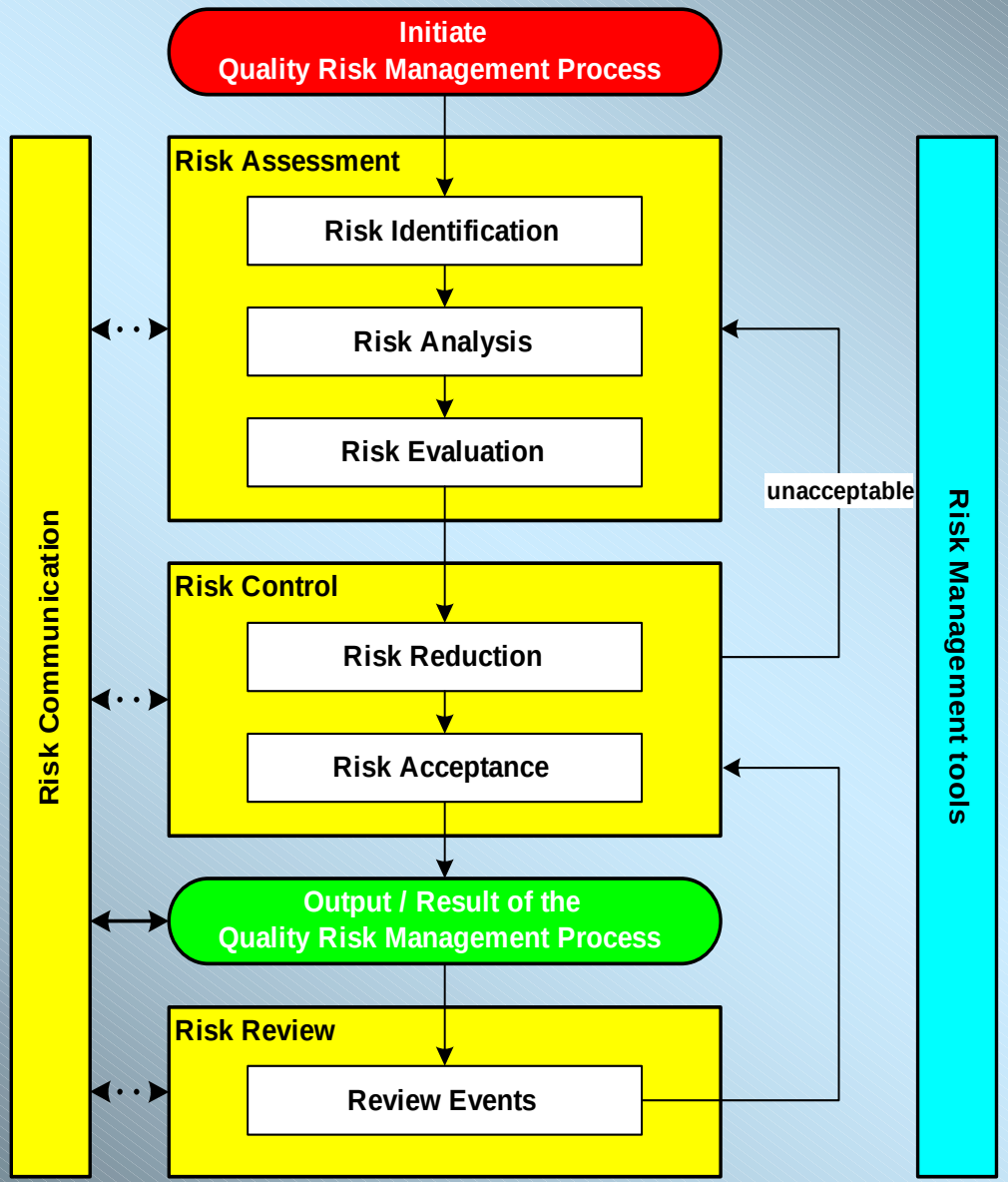
- Open the door for submitting Quality by Design data
- No escalation of requirement
  - Defines Baseline
  - Defines optional opportunities
- Optional Update of P2 for adding knowledge for PAC
- Defines : What is a critical parameter
- Design Space: What is/is not a change
- Regulatory Flexibility
  - Continuous improvement
  - Real time release

Q8 Next steps

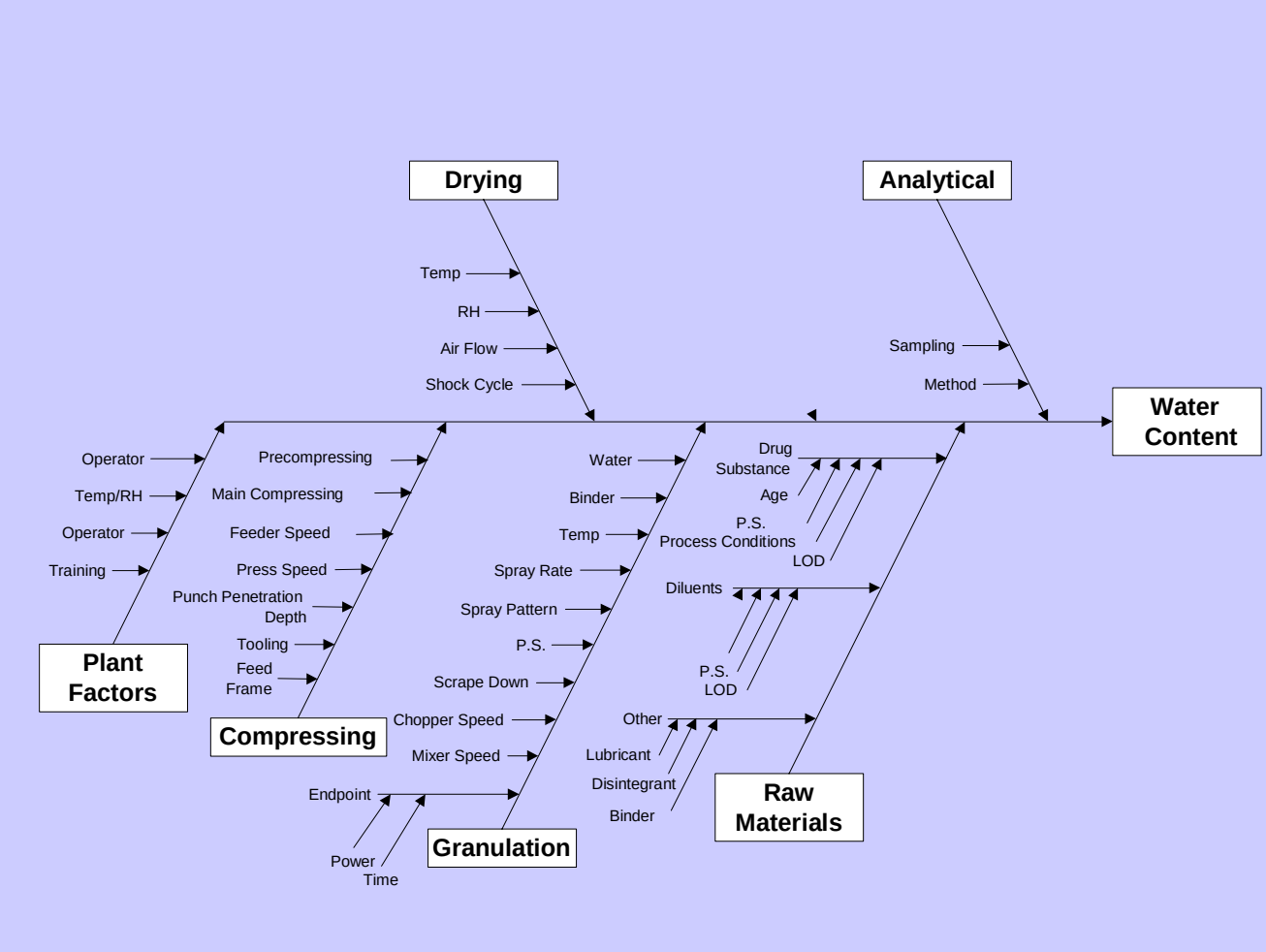
- June 2006 ICH EWG Japan
  - Q8 addendum for specific dosage forms
  - Q8 for API's ?
- Q8 Implementation
  - Learn to use concepts
    - Design space
    - Critical Parameters
    - Regulatory flexibility

Quality Risk Management Q9 and the Control Strategy

The Quality Risk Management Process



Cause and Effect Process



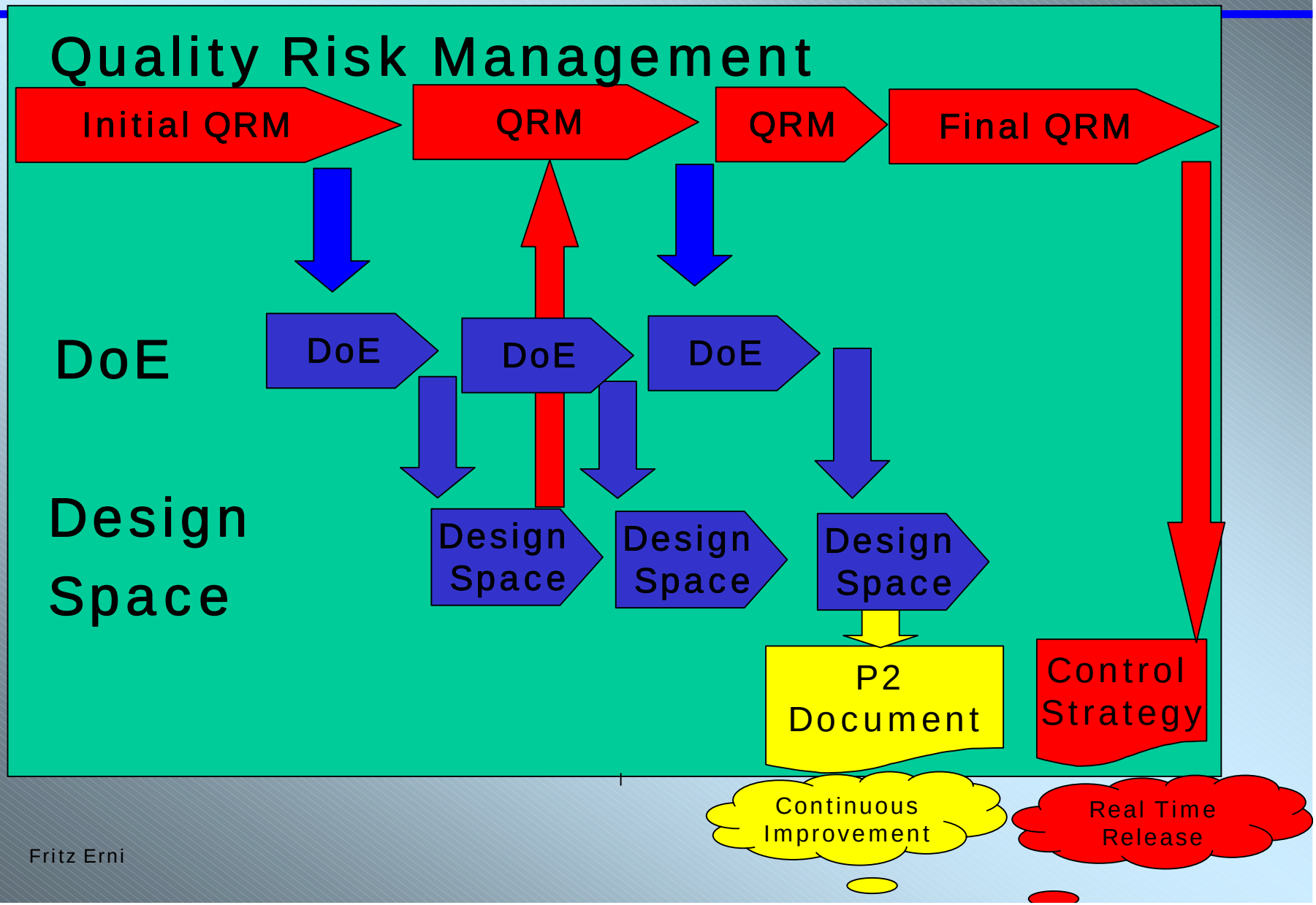
QRM Tools:
Failure Mode Effects Analysis (FMEA)

Risk Assessment						
Sub-Step	**Event (Failure mode)**	**Effect**	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk factor (S*P*D)**
Granulation Drying	water content	not meet specification of degradation	2	3	1	6

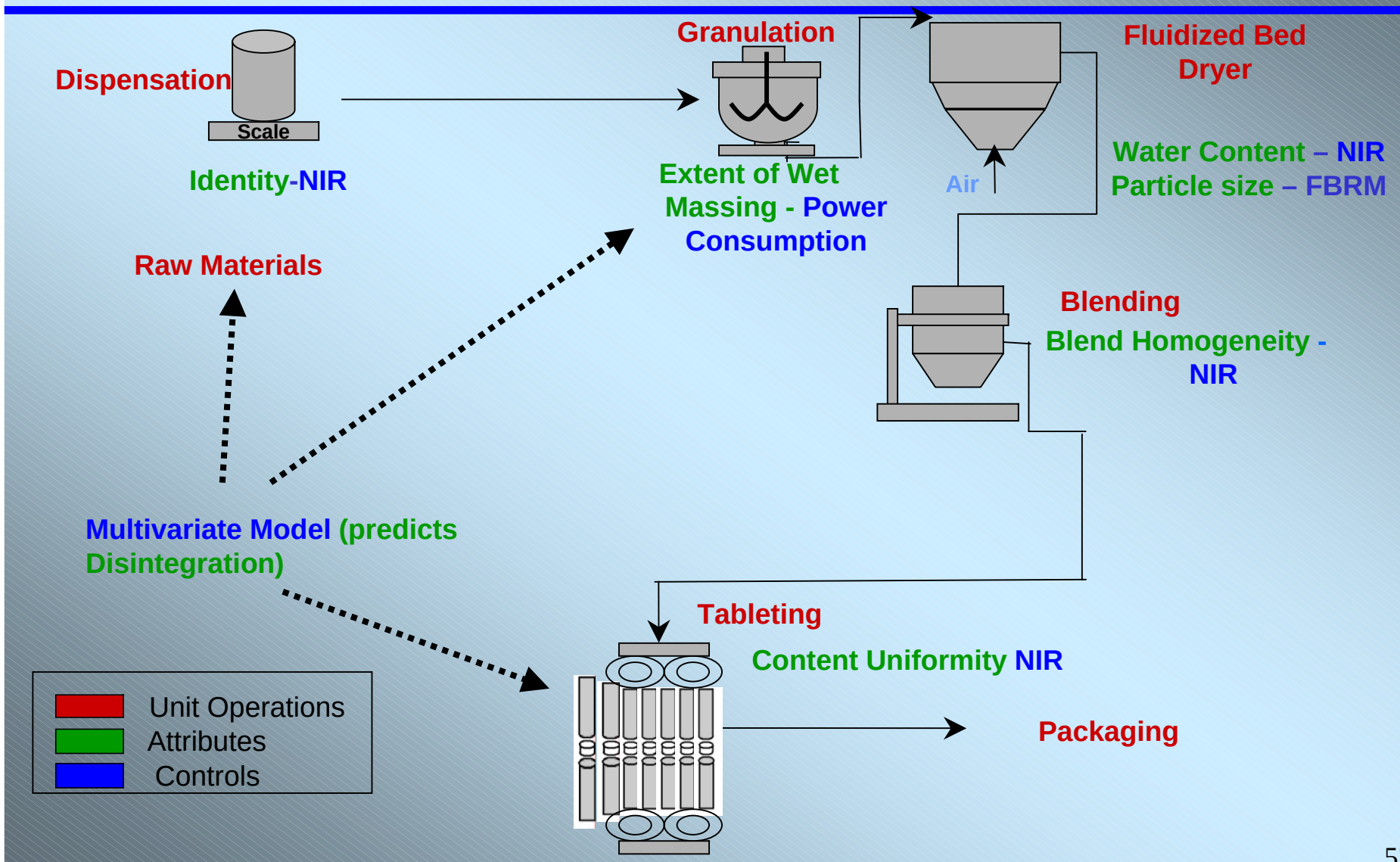
Risk Reduction						
Actions: Risk reduction strategy	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk factor (S*P*D)**	**Risk reduction**	**Comments**
introduce online NIR	2	1	1	2	4	indirect measurment
introduce IPC analytic	2	2	1	4	2	direct measurement; time consuming
humidity measurement in the exausting air	2	1	2	4	2	indirect measurment; unspecifoc

Risk Management process

QRM – Design Space – Control Strategy



Control Strategy



Control Strategy

- Justification of necessary controls
  - Raw Materials Control
  - In-Process Controls
  - End Product Controls (if necessary)
- Based on Process and Formulation Understanding
- Drives the Process in the Design Space
- Based on Quality Risk Management
- To ensure conforming Quality according Specifications

Summary

- Q8 describes content of Section P2 of the Q-CTD
- Q8 is a Door Opener for
  - Describing Quality by Design
  - Including more Science and Risk Management
  - Including PAT
  - Include Design Space
- Introduces the concept of Design Space
- Describes how to define what is critical
- Redefines what is a Change
- Quality Risk Management supports the Control Strategy

EFPIA PAT Topic Group

Chris Potter	AstraZeneca: Chairman
Rafael Beerbohm	Boehringer-Ingelheim
Alastair Coupe	Pfizer
Fritz Erni	Novartis
Gerd Fischer	Sanofi-Aventis
Staffan Folestad	AstraZeneca
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Stephan Roenninger	F Hoffmann-La Roche
Alistair Swanson	Pfizer