PAT and Quality by Design exemplified in a Mock P2 submission for *examplain* tablets

- Part 1: Concept and Principles
- Part 2: Mock P2 Submission

Part 1 – Concept and Principles

- Introduction
- Rationale
- Concept
- Objective
- Mock P2 Document
- Principles
- Example chosen

Introduction
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

Introduction
Mock P2 Document

Not a complete P2 Pharmaceutical Development section

- A simplified case to exemplify fundamental principles and key concepts, promoting discussion
- Focus on regulatory implications of manufacturing concepts of the future
- Quality by Design related to the Target Product Profile
- Demonstration of Risk Management (RM) applied to pharmaceutical development

Rationale

- Current regulatory hurdles in changing without prior approval:
  - Analytical or manufacturing processes
  - Equipment, Sites and Scale
  - Ongoing stability programs
- Use process understanding to derive real time release
- Need examples as basis for discussion and clarification of uncertainties within industry and authorities
- Use as **an example** for future submission documentation (not the only way)
- Foundation laid for the science based discussion

Concept
Assumptions

Mock P2 Document

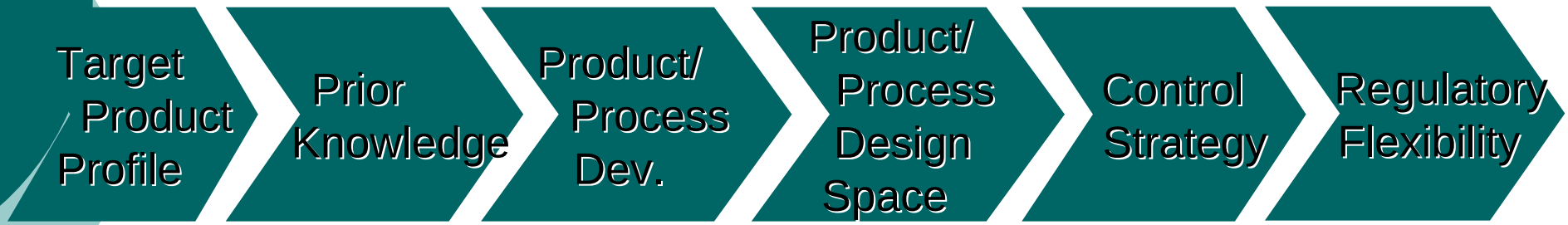
"*Examplain*" chosen as a simple product manufactured with a non-complex process but with a critical to quality attribute.

- New paradigms linked with the application of practical tools and elements, for instance
  - Risk Management tools, rapid on-line measurements of relevant material attributes
  - Continuous verification to replace traditional process validation
  - Models and prediction

Objective
Mock P2 Document

Preparation of a draft document paper based on current industry thinking to enable discussion with authorities and within industry for the implementation of Quality by Design (QbD) and PAT principles in future submission papers focused on the current P2 document content

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)

Mock P2 Document
Structure

- Format CTD / P2
- Type = Mock
- References
  - “Core P2 document only- cross – references to other CTD sections necessary for certain elements (e.g. Method Validation)”
- Content
  - Target Product Profile linked to patient safety and efficacy
  - Risk Management tools
  - Design Space development
  - Rational for Control Strategy and impact on end product testing

Mock P2 Document
Candidate

- As candidate a solid oral dosage form BCS class I containing a well characterised drug substance had been chosen

Target Product Profile:

Description	Round normal convex uncoated tablet
Identification	Positive
Assay	20 mg ± 5% active at time of manufacture
Degradation products	Qualified meeting ICH Q3B and Q6A criteria
Dissolution	Immediate release
Uniformity of dosage units	Meets pharmacopoeial acceptance criteria
Microbiological limits	Meets pharmacopoeial acceptance criteria

"*Examplain*" Tablets
Brief Description

- "*Examplain*" an immediate release solid dosage form
  - Tablet of 200 mg containing 20 mg drug substance
  - Biopharmaceutics Class I (highly soluble, highly permeable)
  - Conventional, wet granulated tablet formulation
  - Some potential for degradation
- Drug substance properties
  - Low bulk density, crystalline, single stable polymorph
  - Primary amine salt

"*Examplain*" Tablets
Brief Description

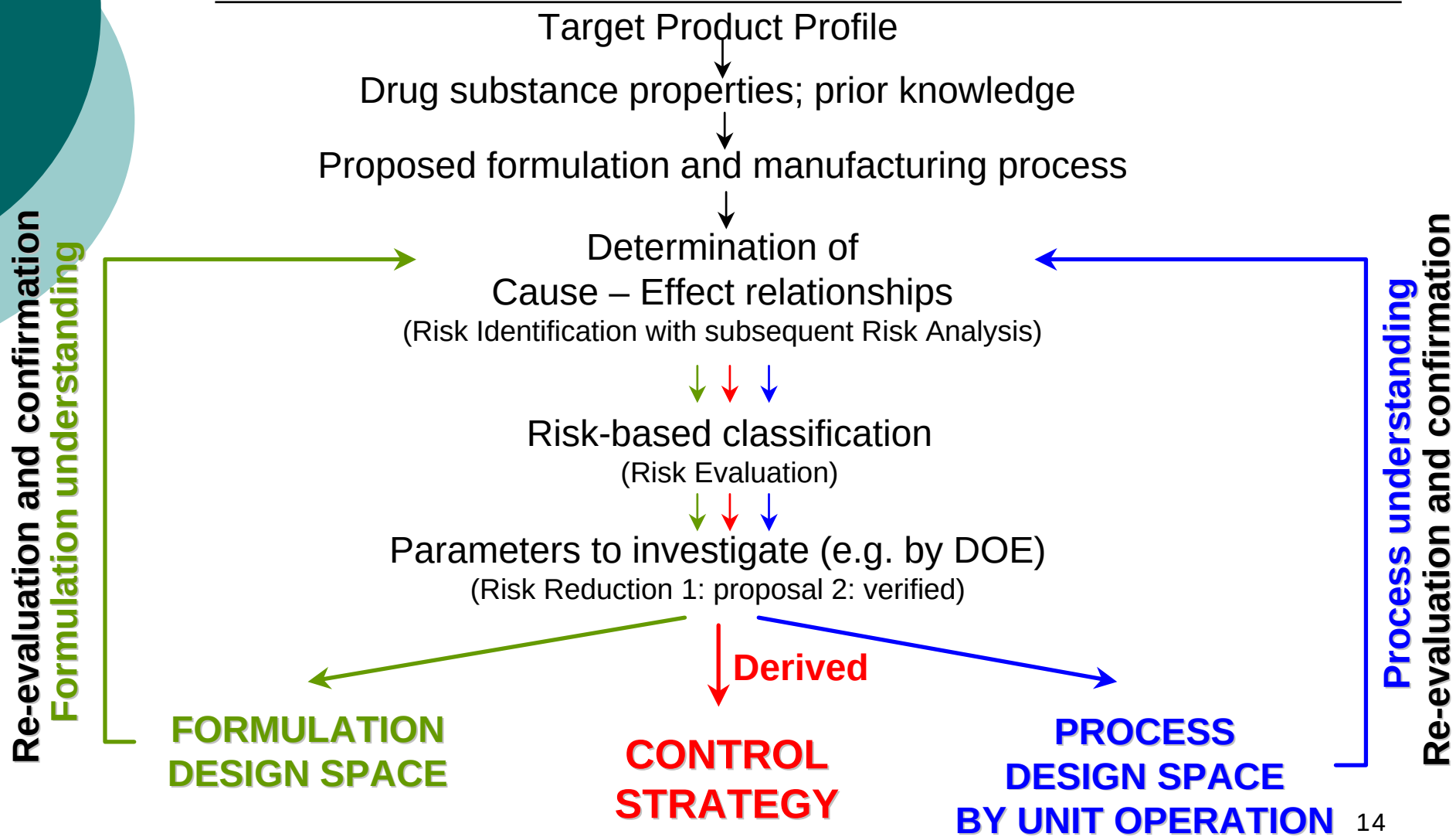
- Identified that fluidised-bed drying is the critical step and the level of hydrolysis product (des-ethyl examplain) is a critical attribute
- Based on development work and mechanistic process understanding Design Space for granulation and fluid bed drying have been developed
- Packaging in Aclar with aluminum layer is sufficient from drug product stability studies
- Removal of end product testing has been derived based on the developed Control Strategy

"*Examplain*" Tablets
Scientific Principles

Principles

- A Control Strategy has been derived after completion of process understanding studies and application of Risk Management tools
- Specifications can be set scientifically based on relationship to safety and efficacy
- Critical to quality steps and attributes are identified
- Regulatory flexibility can be proposed
- Real time release can be justified

Scientific Principles
Iterative Approach

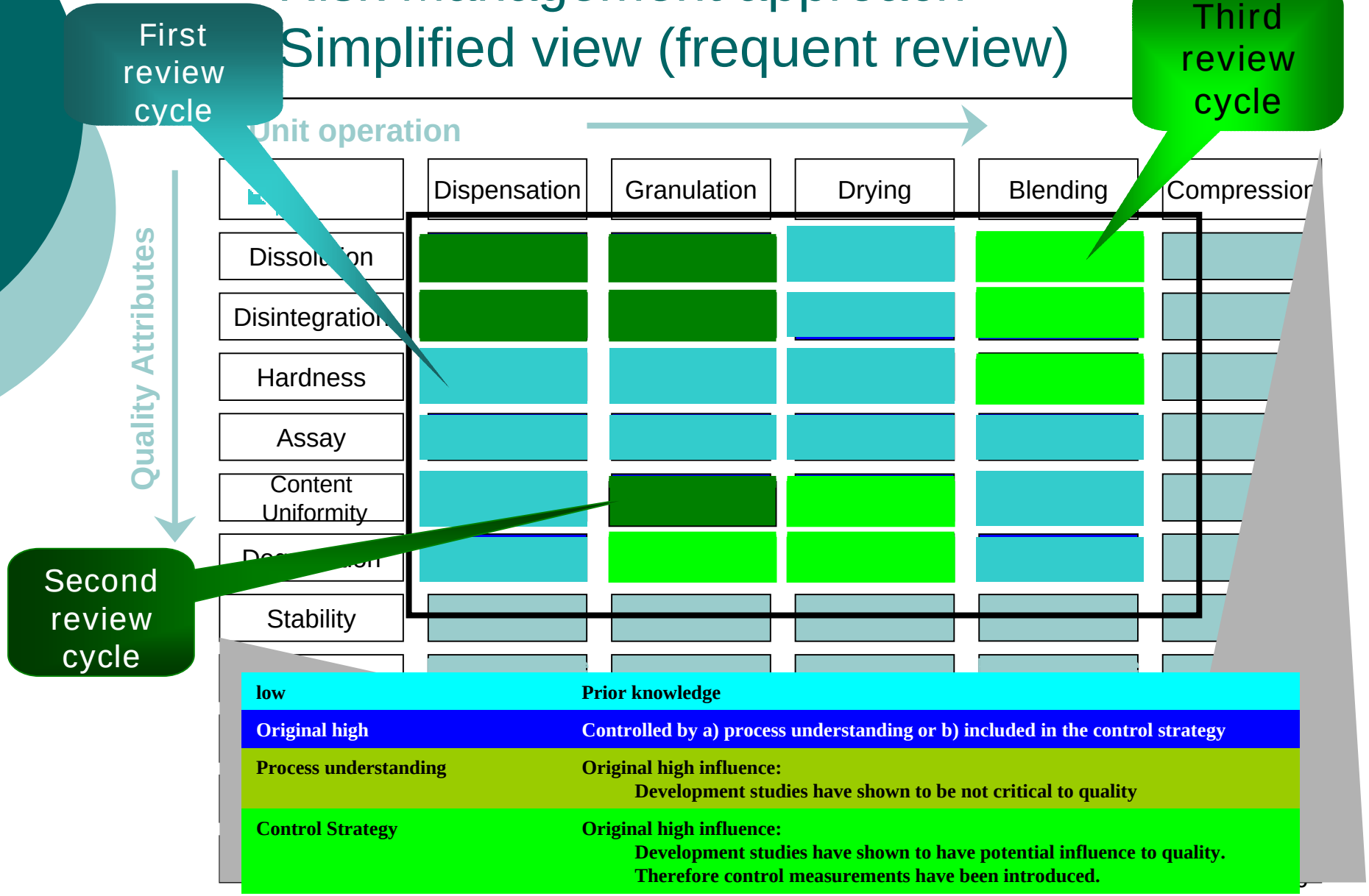


Scientific Principles
Risk Management

Principles

- Risk Management according ICH Q9 approach has been applied
- Prior knowledge, experience from other projects and the application of DoE are the main driver for getting fact-based mechanistic process understanding
- An **initial** risk assessment identifying potential interactions between unit of operations and key attributes is the starting point for the development work
- Risk assessment, control and communication had been constantly updated (reviewed) within the development work
- Tools like e.g. Ishikawa diagram and FMEA have been used for the identification and quantification of risks

Risk Management approach
Simplified view (frequent review)



Part 2 – Mock P.2 Submission

- TPP linked to safety and efficacy
- Initial Risk Assessment
- Formulation Development
- Process Development
  - Granulation
  - Fluid bed drying
- Control Strategy
- Impact on End Product Testing
- Regulatory Flexibility
- Discussion

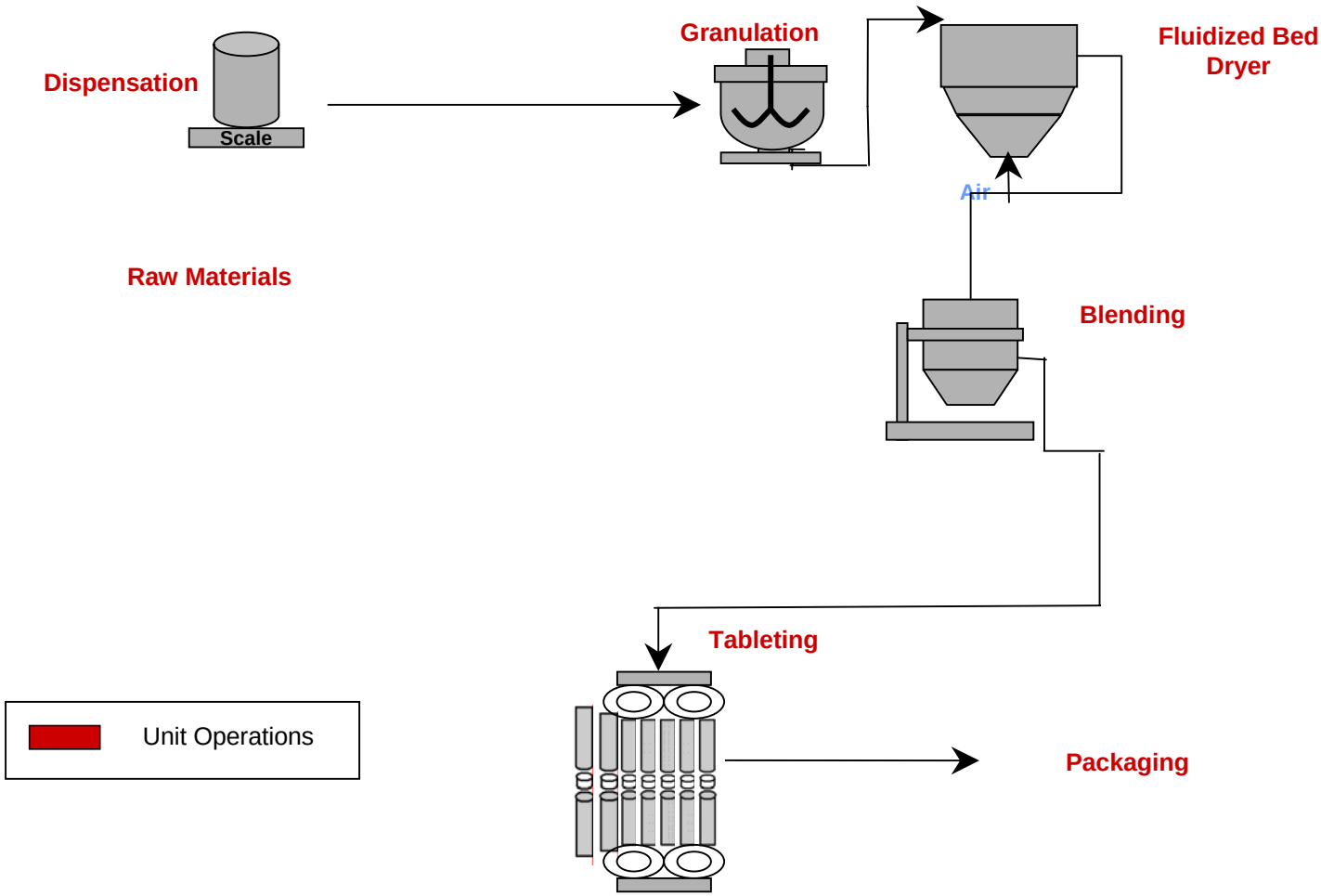
TPP *Examplain* linked to safety and efficacy in patients

- TPP summarises the quality attributes of the product required to meet the needs of the patient for safety and efficacy
- Safety is primarily assured by des-ethyl examplain being less than 2% at the end of shelf life
  - Limit has been qualified in toxicological studies
  - Pharmacopoeial ranges for acceptable uniformity of content are much less than that seen for variability of plasma levels in Phase 2 and Phase 3 clinical studies
  - Appropriate GMP standards during manufacture assure microbiological quality of this orally administered drug
- Efficacy is assured for this BCS Class I drug substance by application of a dissolution test during development*
- Efficacy is assured by application of a lower limit for uniformity of dosage units (similar to the safety justification)

*FDA Guidance for Industry-'Biowaver Guidance', CDER 2000 has been applied

Introduction

Manufacturing Process (simplified scheme)



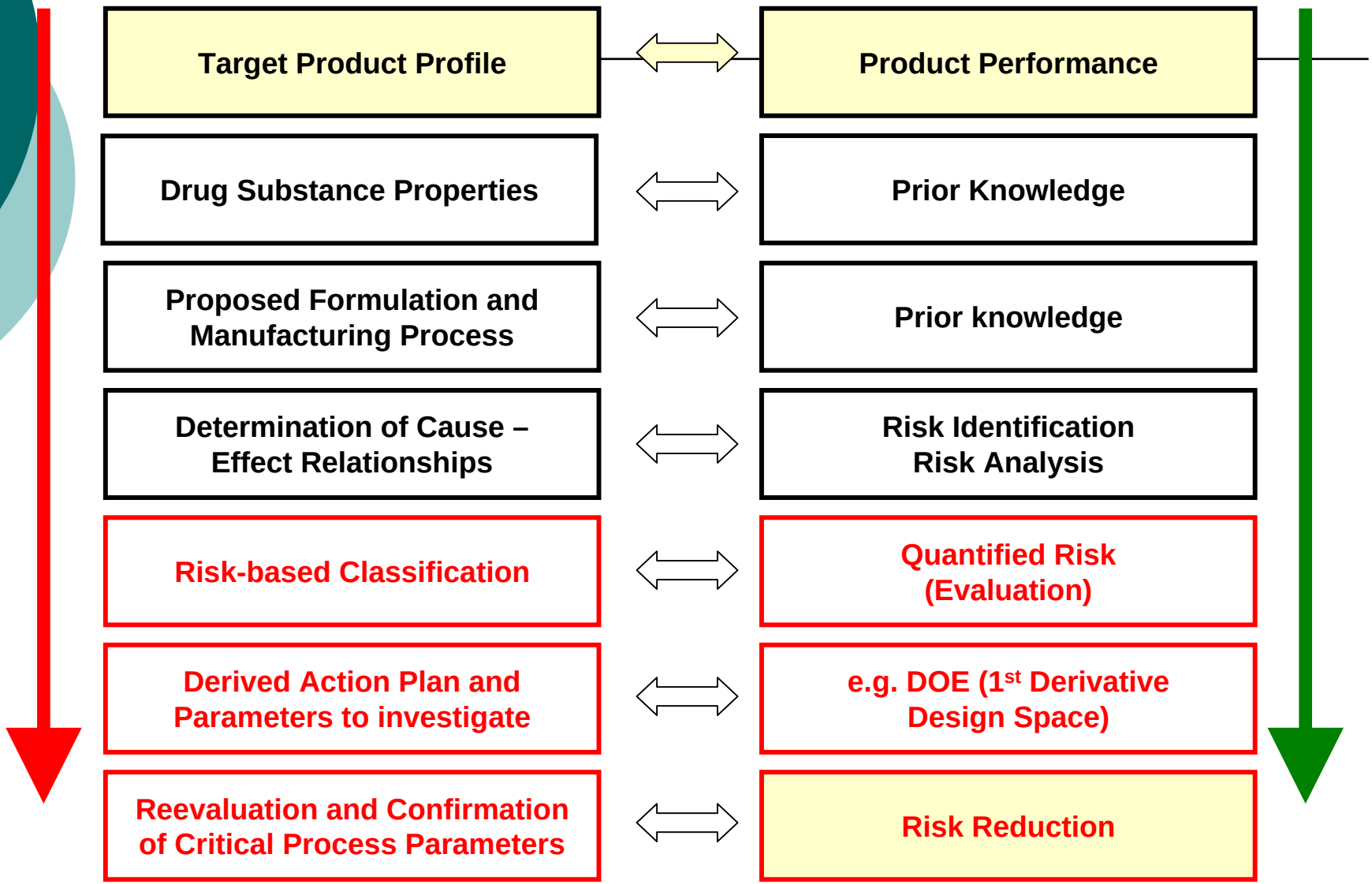
Initial Risk-Based Classification:
Impact of Unit Operations on Quality

Unit operations / Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution			Prior knowledge			Prior knowledge
Disintegration			Prior knowledge			Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge			Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge		Prior knowledge
Content uniformity	Prior knowledge					Prior knowledge
Degradation	Prior knowledge			Prior knowledge	Prior knowledge	
Stability	Prior knowledge	Prior knowledge		Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge		Prior knowledge		Prior knowledge
Identification		Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge		Prior knowledge	Prior knowledge	
Microbiology			Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

Conclusion from initial risk evaluation
DOE Plan Formulation Development

- Factors to study:
  - Drug substance particle size
  - Selection of other raw materials (lactose vs. mannitol) and ranges (e.g. magnesium stearate)
  - Hardness of tablets
  - Tablet dissolution
  - Evaluation of water content in tablets
  - Initial evaluation of content uniformity

Pharmaceutical Development – Transformation into Practice



Formulation Development
Drug Substance Particle Size

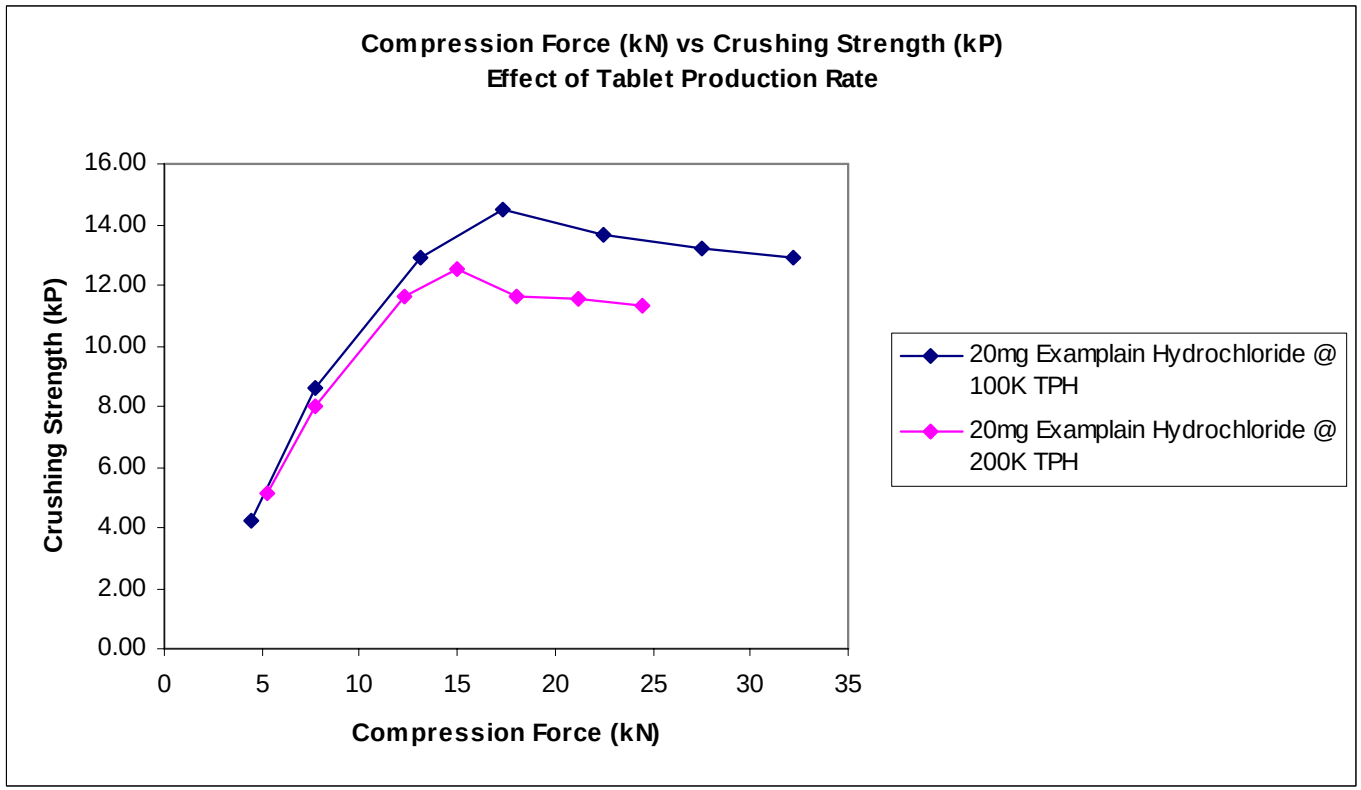
- Due to the basic nature of *examplain* (pKa = 10.1 in aqueous solution at 25ºC), the solubility is greatest at low pH values and begins to drop as the pH rises.
- Tablets manufactured from drug substance with small (d_{90} < 15 µm, d_{10} < 5 µm) and large (d_{90} < 180 µm, d_{10} < 30 µm) particles showed essentially equivalent dissolution performance (Chapter: 3.2.P.2.1.1;Figure 3).

Formulation Development
Raw Material Selection

- Examplain hydrochloride was shown to be incompatible with lactose, as expected due to the ability of the primary amine in the drug substance to undergo a Maillard reaction.
- No evidence was seen for degradation of drug substance in the presence of microcrystalline cellulose, mannitol, dibasic calcium phosphate, povidone K-30, hydroxypropylmethyl cellulose, croscarmellose sodium or magnesium stearate.
- The binder concentration in range of 4% and 6% has no significant effect on tablet dissolution or disintegration.

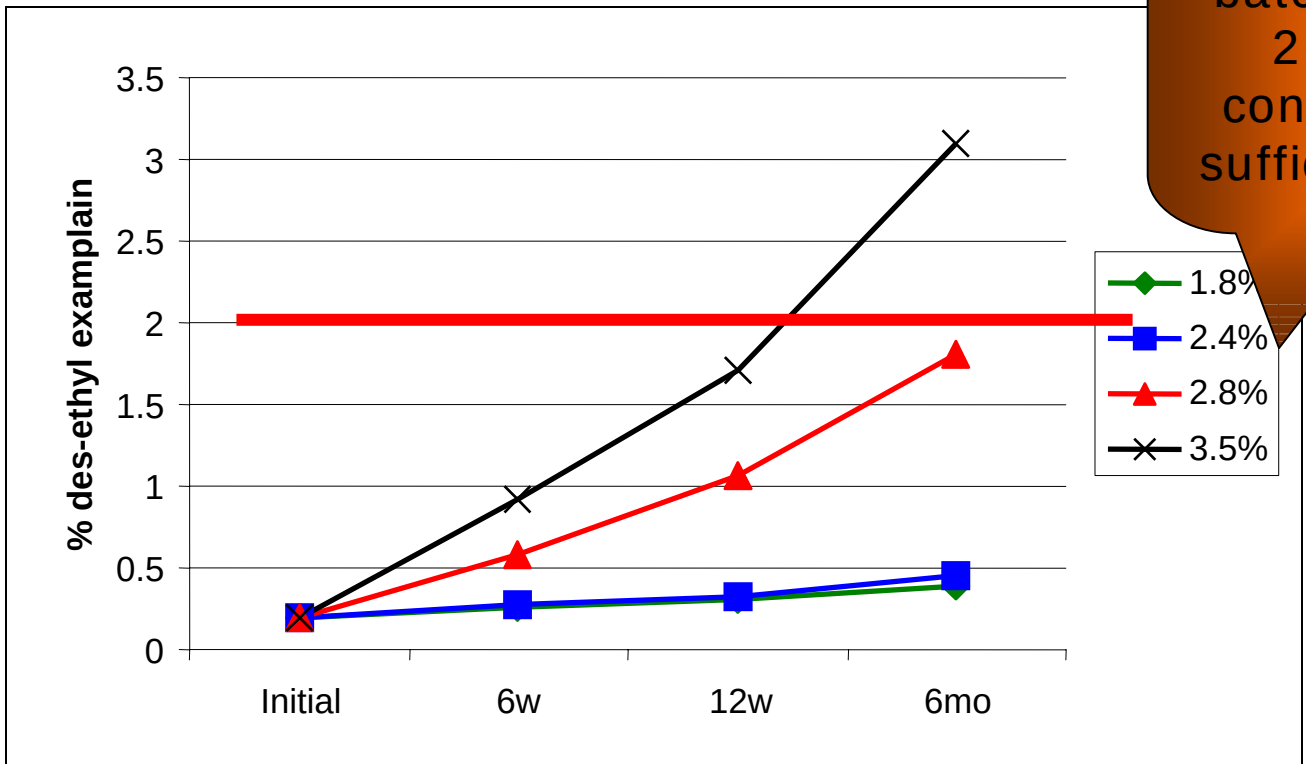
Formulation Development
Hardness of Tablets

- Hardness above or equal 4 kP produces acceptable tablets



Formulation Development
Water Content

- Studies show that a maximum water content of 2%w/w in tablets produces acceptably stable drug product



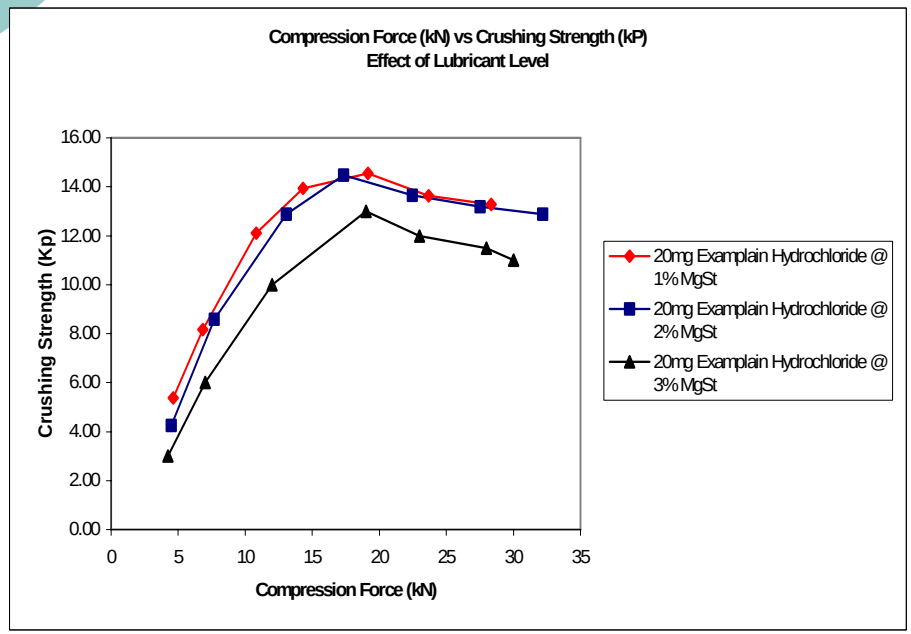
One stability batch containing 2.4% water content showed sufficient stability

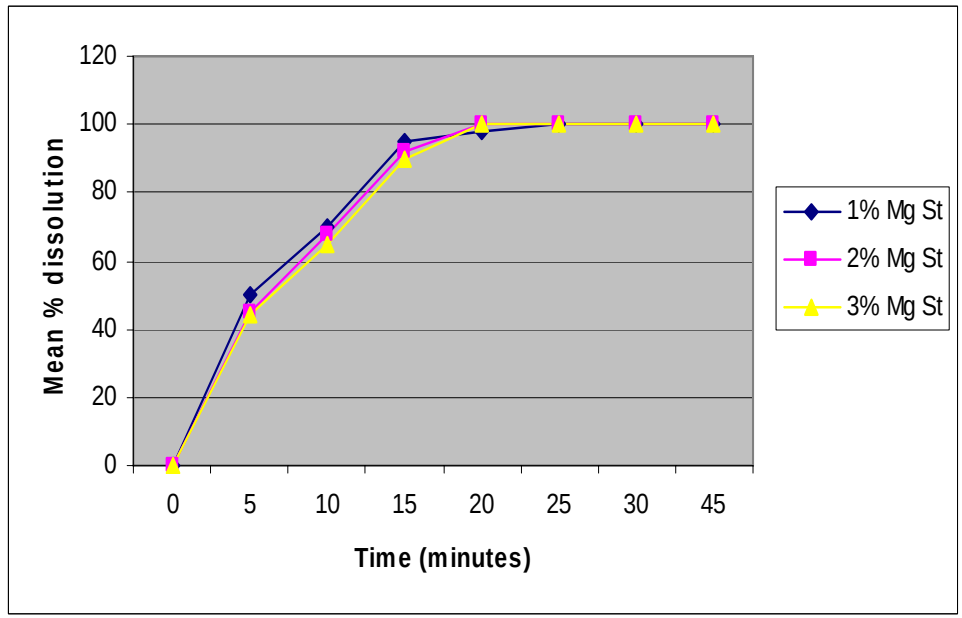
Formulation Development
Water Content /Packaging material

- Aclar as foil for unit dose blisters (aluminium foil backing) showed improved stability compared with unpacked tablets after storage at 40°C/75% RH for 6 months
  - The batch of tablets contained 2.4% moisture content.

Formulation Development
Magnesium Stearate Concentration

- In the range of 1% to 3% no significant effects on compression or dissolution at this level have been demonstrated





First Review of Risk Assessment

Unit operations / Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution	Fig 3 (Particle size API)		Prior knowledge	Fig 9	Fig 9	Prior knowledge
Disintegration	Fig 3 (deduced)		Prior knowledge	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge	Fig 8	Fig 7	Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge		Prior knowledge
Content uniformity	Prior knowledge					Prior knowledge
Degradation	Prior knowledge			Prior knowledge	Prior knowledge	
Stability	Prior knowledge	Prior knowledge	Water content less than 2% based on Formulation Development	Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge		Prior knowledge		Prior knowledge
Identification	Based on Control Strategy	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge	To be controlled	Prior knowledge	Prior knowledge	
Microbiology	Specification of starting material		Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

Formulation Development
Conclusions

- A dissolution test has been developed, which is an excellent surrogate for in vivo absorption
- Design Space boundaries for Mg stearate concentration are 1% and 3%
- Development studies showed relationship between water content, degradation, and stability as critical
  - further study during process development and consideration in the control strategy
- Manufacturing process development has to cover further potential interactions not evaluated by formulation development (next slide)

Process Development
Next Steps

- Process Development focussed on evaluation of unit operations and their impact on quality attributes
  - Granulation – content uniformity, dissolution / disintegration
  - Drying – water content, content uniformity
  - Blending – content uniformity
  - Tableting – assay, content uniformity
  - Packaging – water content

Process Development
Granulation

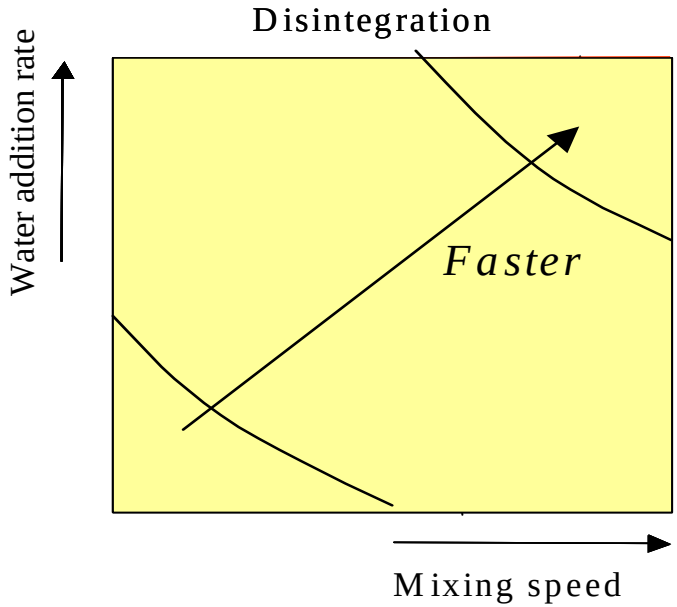
- All parameters relevant to wet granulation were identified from the Ishikawa diagram and introduced into a detailed risk assessment (FMEA)
  - To establish those process parameters associated with the critical to quality attribute, water content
- Process understanding generated through prior knowledge, experimental development data (DoE studies at 1Kg and 25 Kg scale) and use of multivariate experimental plans with in-line analytical applications

Process Development
Key Process Variables for Wet Granulation

- Based on general process experience and prior knowledge the following key process variables will be considered in DOE studies for *examplain*

Wet granulation parameters	**Input material attributes**
Mixing speed	API particle size
Water addition rate	Mannitol particle size
Mixing time	

Process Development
Influence of Mixing Speed & Water Addition Rate on Disintegration

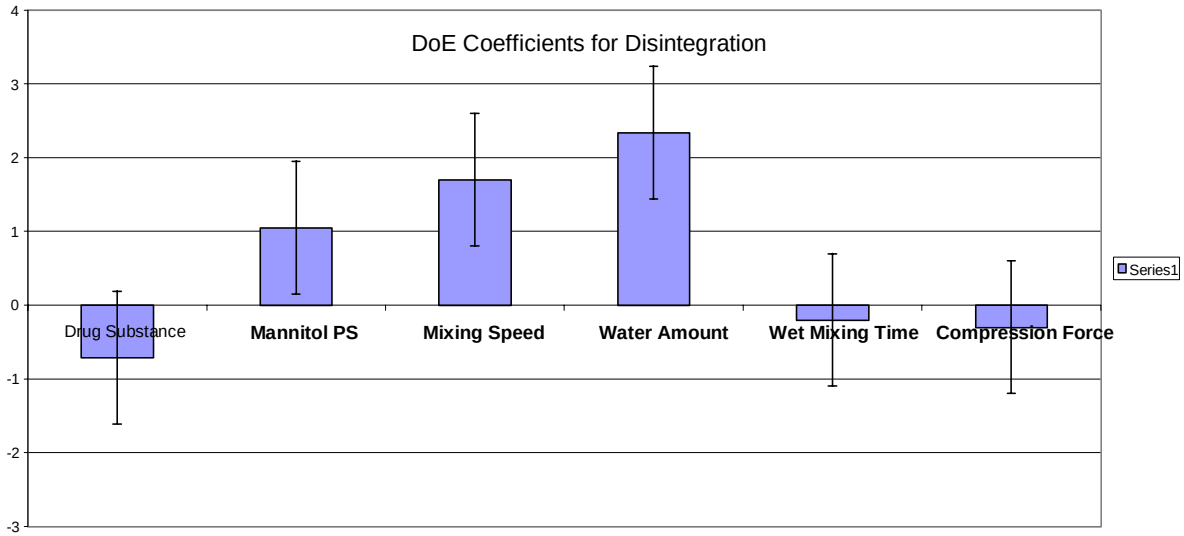


yellow = meets pharmacopoeial quality requirements for an immediate release dosage form

- These DOE studies showed that factors like mixing speed and water addition rate are the most important on disintegration

Process Development
DOE Coefficients for Disintegration

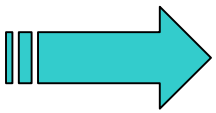
- Relative Importance of Process Parameters on Disintegration could be derived from evaluation of Coefficient Plot from Partial Least Squares (PLS) Model (Data out of DoE studies)



Key process variables could be confirmed with no significant influence on disintegration

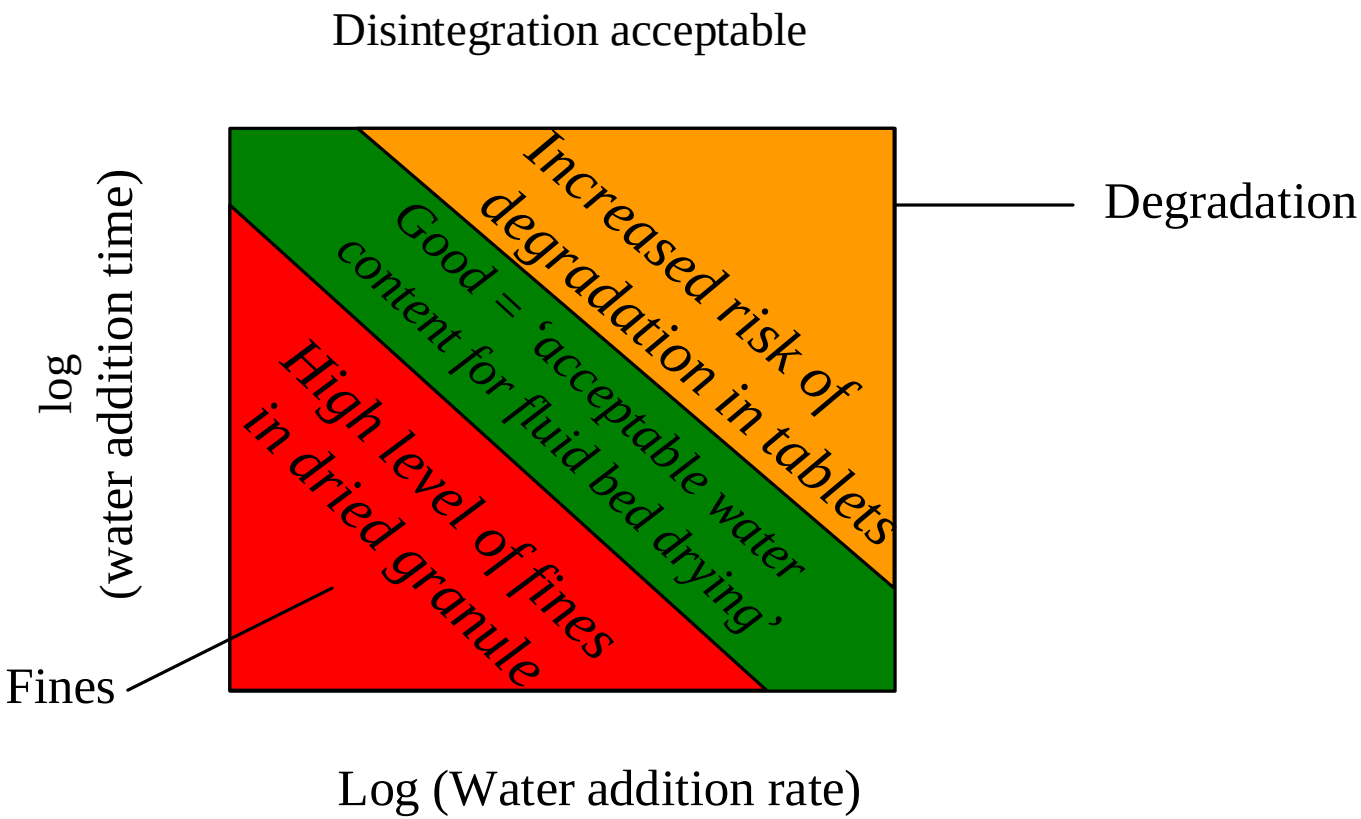
Process Development
Summary

- Water addition rate and time can be continuously adjusted within the design space to obtain highly consistent granule properties mainly with respect to flowability, compressibility, degradation, and suitability as input to the next processing step



This acceptable region could be considered as the Design Space for water addition rate and time (see graphical presentation)

Process Development
Summary



Design Space for water addition rate

Design Space for Wet - Granulation
Summary

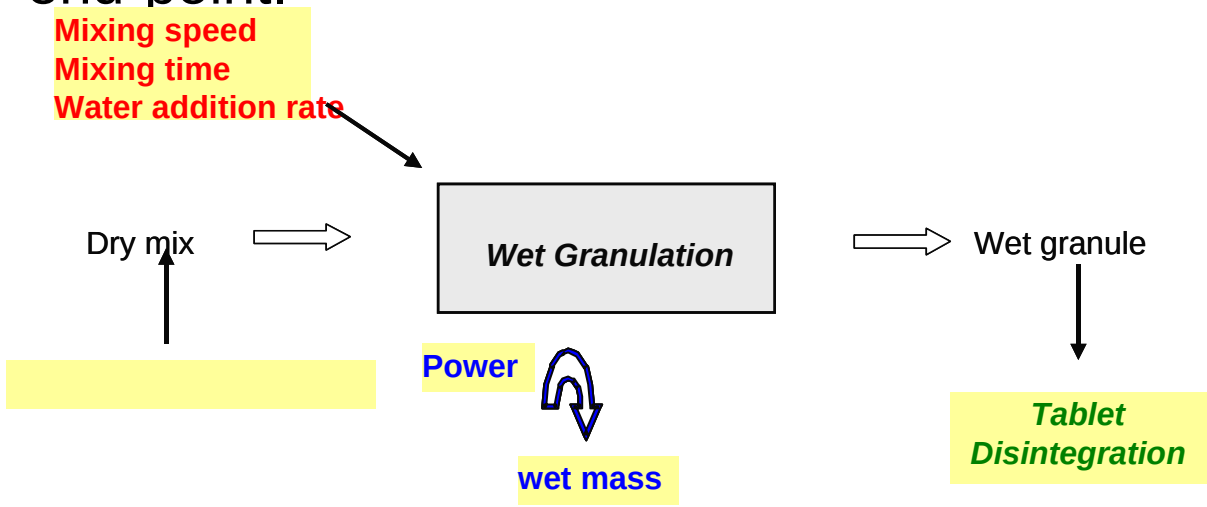
- Multivariate for tablet disintegration, content uniformity and degradation parameters
  - Water addition rate
  - Mixer speed
  - Time
- Output optimised for water content for drying
- Could use multivariate model to predict disintegration
- Change of scale can be understood
- Area of failure not always found (disintegration)

Second Review of Risk Assessment

Unit operations/ Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution	Fig 3 (Particle size API)	see 3.2.P.2.3.1.	Prior knowledge	Fig 9	Fig 9	Prior knowledge
Disintegration	Fig 3 (deduced)	see 3.2.P.2.3.1.	Prior knowledge	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge	Fig 8	Fig 7	Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge		Prior knowledge
Content uniformity	Prior knowledge	????				Prior knowledge
Degradation	Prior knowledge	see 3.2.P.2.3.1.		Prior knowledge	Prior knowledge	
Stability	Prior knowledge	Prior knowledge	Water content less than 2% based on Formulation Development	Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge		Prior knowledge		Prior knowledge
Identification	Based on Control Strategy	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge	To be controled	Prior knowledge	Prior knowledge	
Microbiology	Specification of starting material		Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

Control Strategy
Monitoring of Granulation

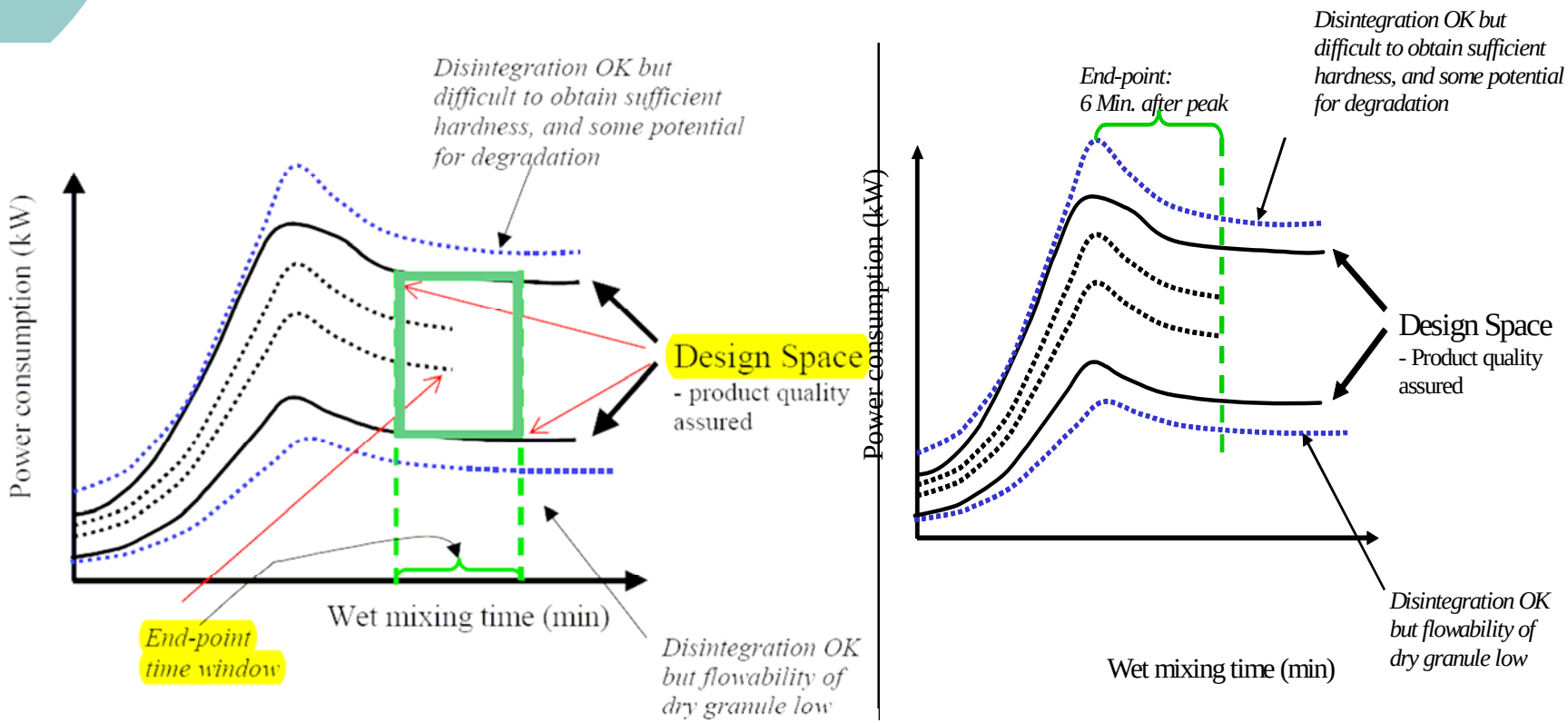
- Monitoring the high shear mixing process by power consumption or other techniques such as acoustic spectroscopy offers PAT opportunities for better process understanding and advanced control, e.g. of end-point.



Red – input variables Green – derived parameters Blue – in-line measurements

Control Strategy
Process Trajectories for Wet Granulation

- Process trajectories based on power consumption monitoring are established on 1 kg scale and confirmed on 25 kg scale.



Control Strategy
Granulation

- The granulation process is controlled by measuring the power consumption during granulation
- The water amount per mass of granulate and the addition feed rate are fixed based on our process understanding (DOE)
- Power consumption peak as starting point for 6 min. interval to finish wet massing (compensates raw material properties (e.g. water content, particle size distributions)
- The wet granulation Design Space is part of the control strategy to provide additional assurance of satisfactory granulation

Process Development
Fluid-bed Drying

- Detailed risk assessment (FMEA) identified fluid bed drying as a possible critical process step with respect to:
  - Water content
  - Des-ethyl examplain impurity level of NMT 2% at the end of shelf life
  - Ensuring disintegration and dissolution characteristics
  - Content uniformity

Process Development

Fluid-bed Drying

- Based on prior knowledge the impact of high level of fines could result in:
  - poor flow during tabletting
  - increased variability in unit dose mass
  - content uniformity
  - effect on disintegration or dissolution
- Water content of up to 2% w/w in tablets produces acceptable drug product stability
  - Water content does not change after granulation upon tabletting and packing
- Over-drying generated increased levels of fine particles

Should be investigated within the development work

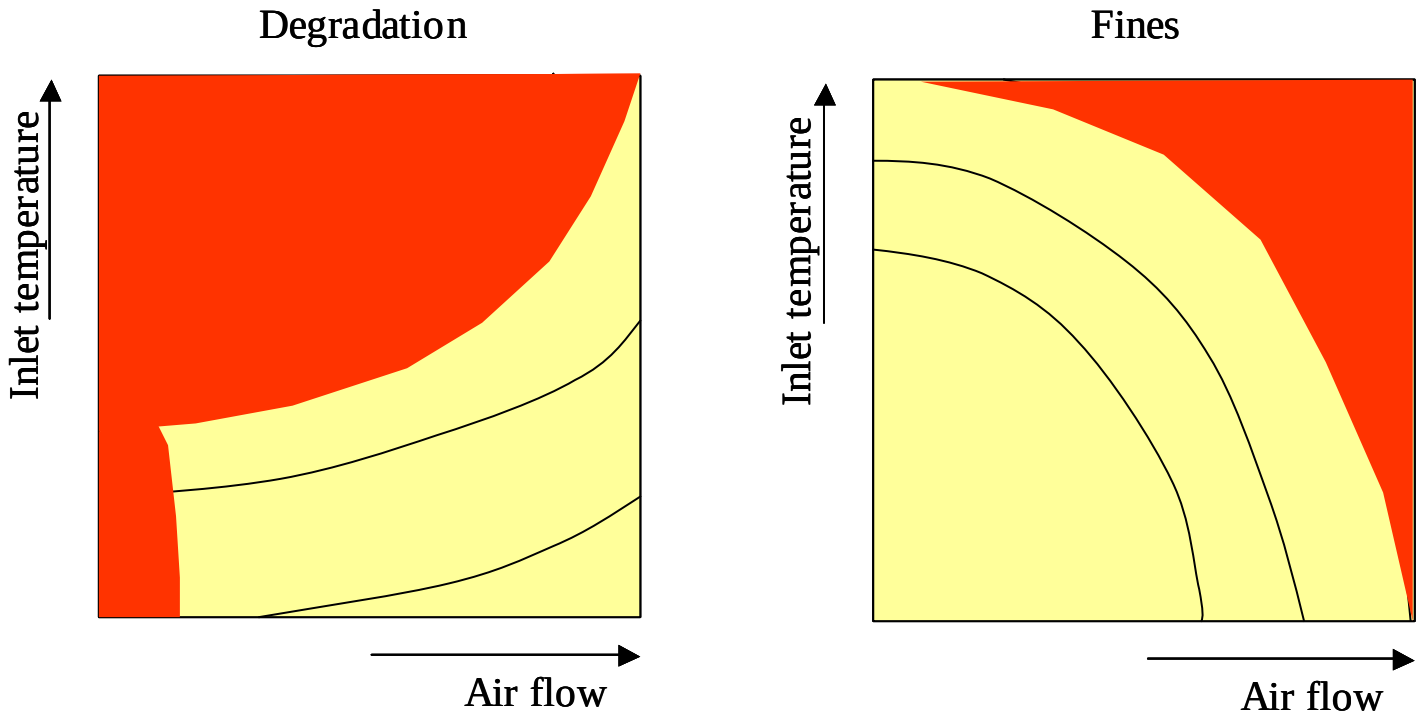
Process Development
Key Process Variables for FBD

Process variables	
Drying parameters	**Input material attributes**
Inlet air temperature	Water content
Inlet air humidity	Granule particle size distribution
Air flow rate	
Fill level	
Filter sock cycle	
Heating rate	
Cooling rate	
Quality attributes	
Dried granule	**Tablet**
Particle size distribution (fines)	Disintegration
Water content	Dissolution
Degradation (des-ethyl examplain)	Weight uniformity
	Content uniformity

Process Development
DOE Plan

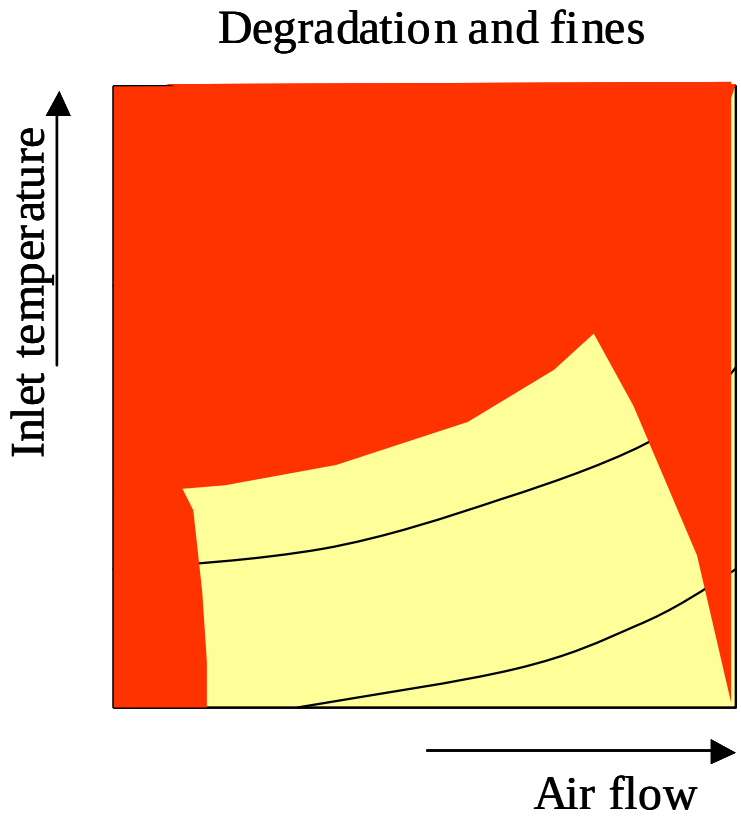
- Established relationships between process variables and quality attributes of the dried granule
  - including equipment settings and attributes from the input wet granules
  - 1 kg scale
  - Monitoring conventional equipment parameters (inlet, bed and outlet temperatures, air flow etc)
  - Additional on-line NIR spectroscopy and Lasentec FBRM methods to measure water content and particle size distribution

Process Development
Degradation and generation of fines

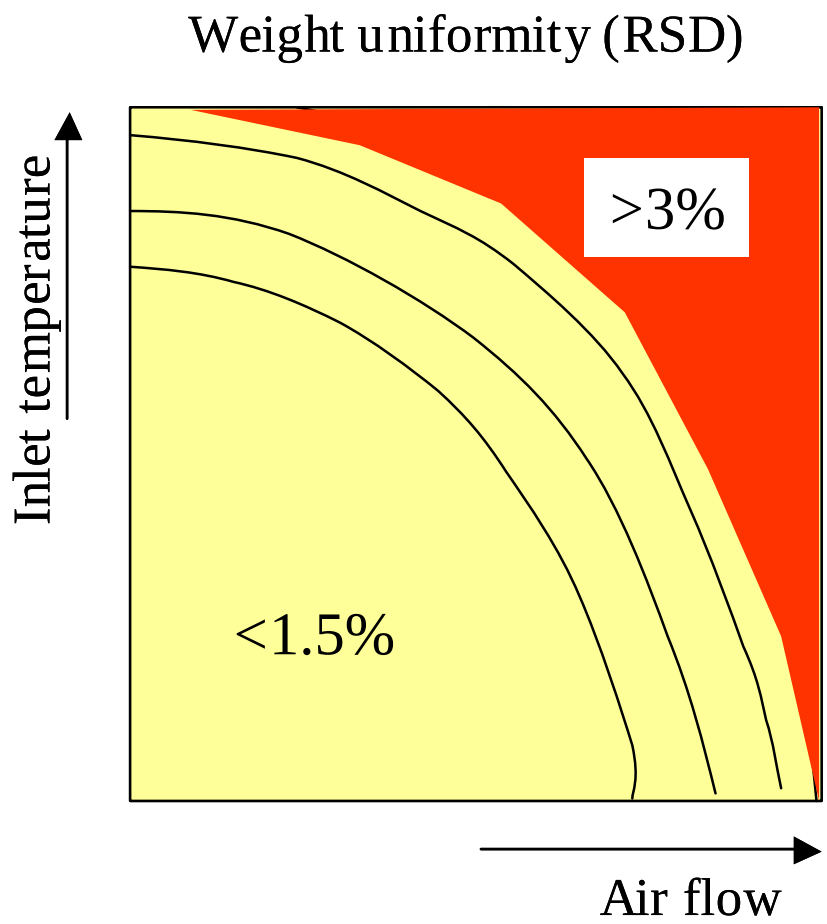


Red = does not meet quality requirements
1 kg scale

Process Development
Combination of Failure Modes



Process Development
Tablet Weight Uniformity

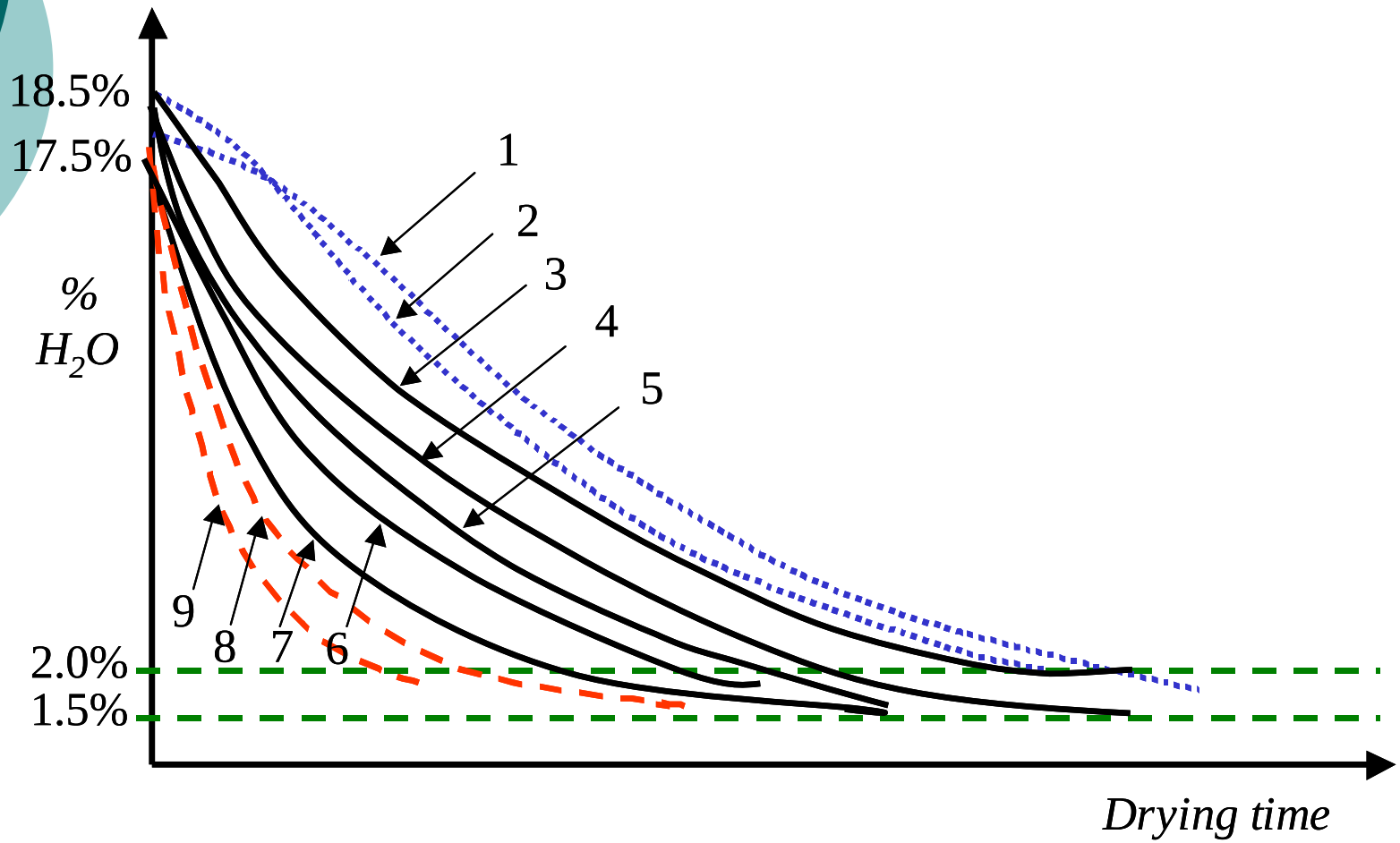


Process Development
Drying Curves

- Drying experiments at 1 kg scale
  - Using wet granulate with water content of 18±0.5% (as is routinely produced by the granulation process)
  - Inlet temperature and air flow were varied
  - Stopped when the water content was in the range 1.5-2.0%
  - Water content of the granules, and their particle size distribution were monitored on-line
- Confirmed at larger scale
- Experiments do not take account of time

Process Development

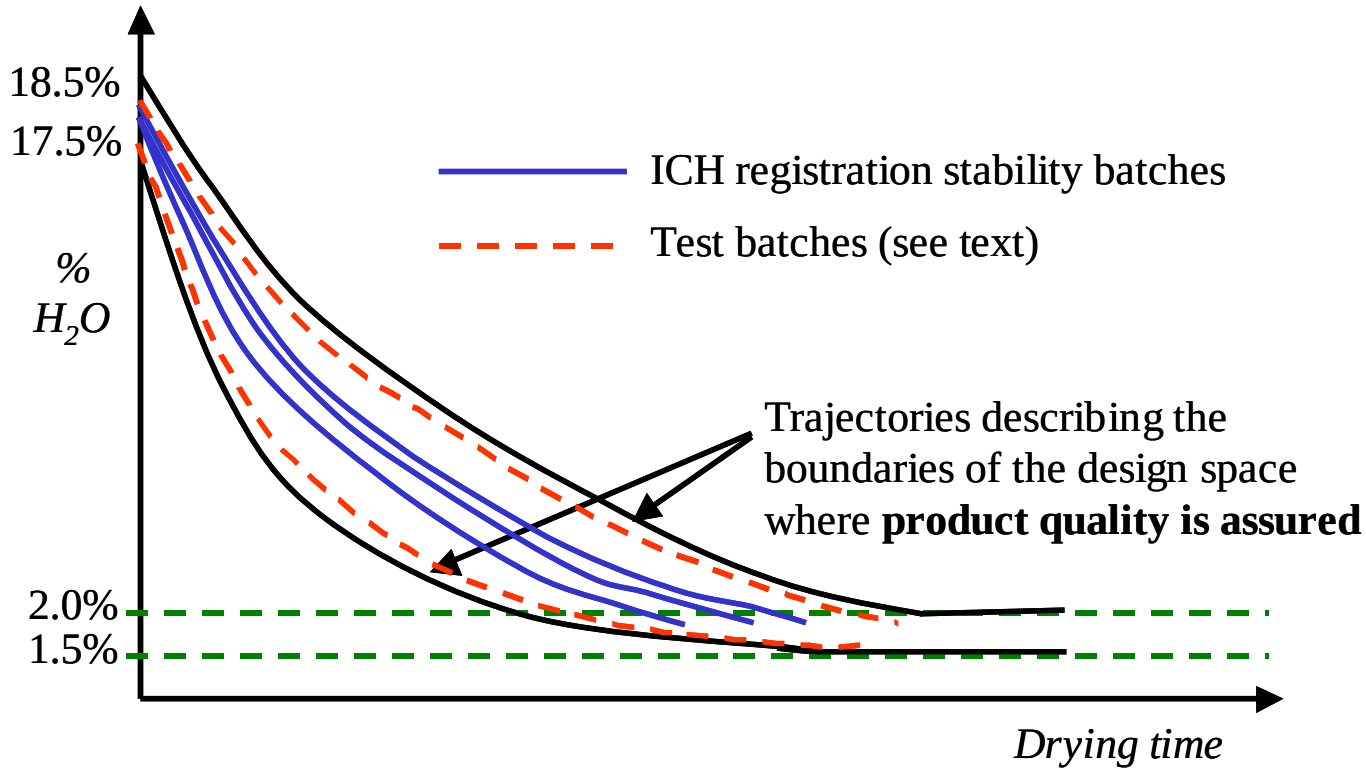
Drying Process Trajectories (1 kg Scale)



Process Development
Drying Process Trajectories – Summary

Experiment / Process Trajectory	% des-ethyl examplain (<1.0%)	% fines (< x µm) (<15%)	Weight uniformity (RSD)	Acceptable quality?
1	1.7	4	1.3%	No – high des-ethyl level
2	1.3	7	1.7%	No – high des-ethyl level
3	0.3	5	1.5%	Yes
4	0.3	5	1.4%	Yes
5	0.2	6	1.7%	Yes
6	0.3	4	1.3%	Yes
7	0.2	7	1.6%	Yes
8	0.2	17	3.4%	No – poor flow impacts weight uniformity
9	0.2	20	5.3%	No – poor flow impacts weight uniformity

Process Development
Drying Process Trajectories (25 kg Scale)



Fluid-bed Drying
DOE Results

- Confirmed the existence of two failure modes
  - degradation / hydrolysis of the API (linked to granule water content)
  - generation of fines (by breaking down the granules)
- Impact of inlet temperatures and flow rates on the amount of degradation and level of fines
  - different combinations of these parameters are required to avoid each failure mode
  - control of granule water content alone is not sufficient

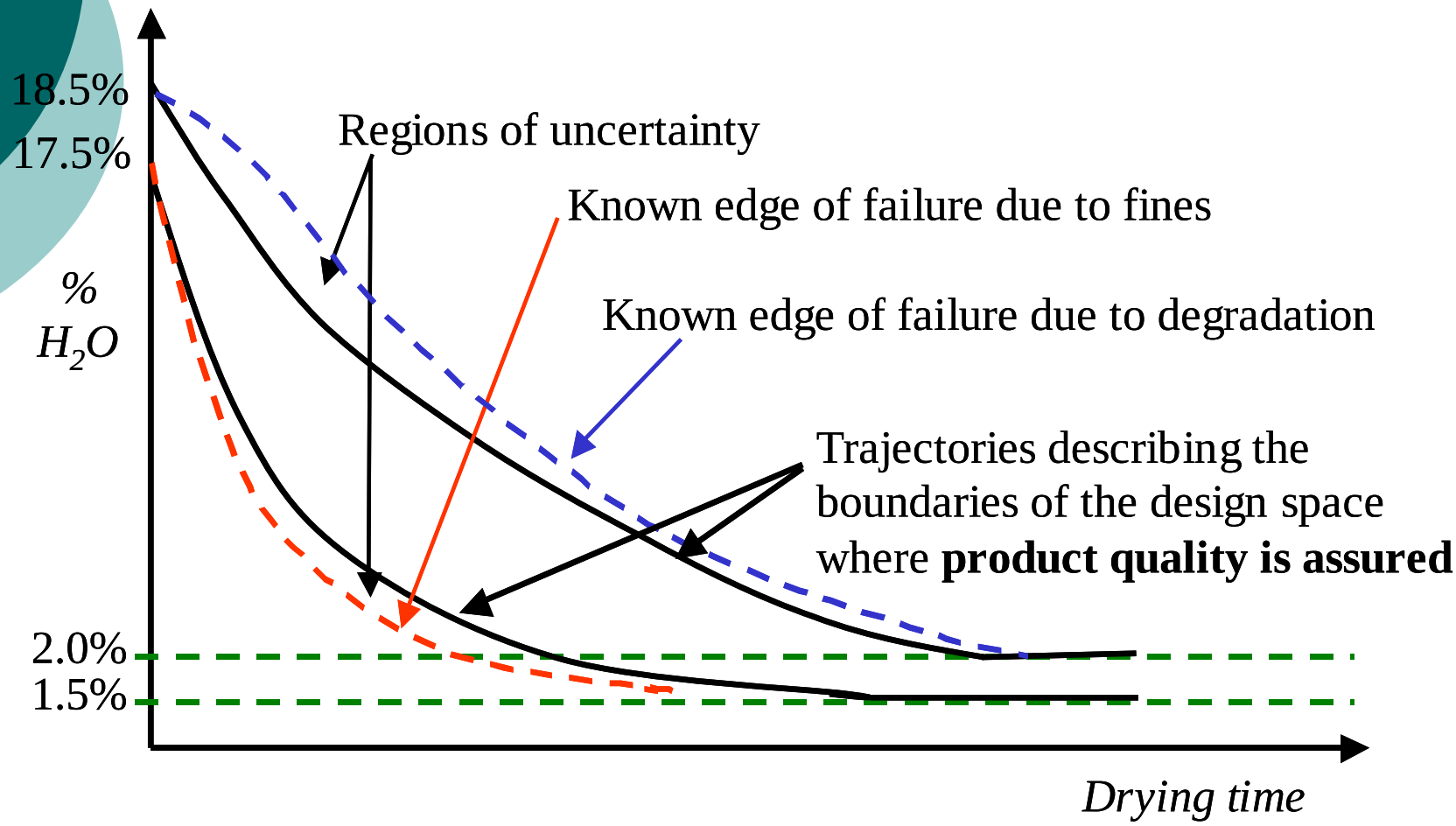
Fluid-bed Drying
DOE Results

- Strong interaction between the effects of inlet air temperature and flow rate on granule properties is consistent with previous experience
- Granule quality is sensitive to
  - inlet air temperature and flow rate
  - water content
  - particle size distribution of the in-going wet granulate
- Inlet air humidity is not critical

Design Space for Fluid Bed Drying
Summary

- Multivariate for degradation, disintegration, uniformity of content
  - Inlet temperature
  - Air flow
  - Drying time
- Trajectory for water content, a critical parameter
- Change of scale understood
- Areas of failure found in this case
- Clear control strategy

Design Space for Drying
Graphical Description



Fluid-bed Drying
Summary

- Two failure modes, one of which also impacts down-stream processing
  - hydrolysis of the API (degradation to des-ethyl examplain)
  - decreased tablet weight uniformity resulting from poor granule flow associated with the generation of fines.
- The disintegration and dissolution properties of the examplain hydrochloride tablets are insensitive to the drying operation
- Design Space established independent of scale

Third Review of Risk Assessment

Unit operations / Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution	Fig 3 (Particle size API)	see 3.2.P.2.3.1.	Prior knowledge No significant effect based on Formulation Development	Fig 9	Fig 9	Prior knowledge
Disintegration	Fig 3 (deduced)	see 3.2.P.2.3.1.	Prior knowledge No significant effect based on Formulation Development	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Fig 9 & 3.2.P.2.1.1 & 3.2.P.2.2.3 (deduced)	Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge	Fig 8	Fig 7	Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge		Prior knowledge
Content uniformity	Prior knowledge					Prior knowledge
Degradation	Prior knowledge	see 3.2.P.2.3.1.		Prior knowledge	Prior knowledge	
Stability	Prior knowledge	Prior knowledge	Water content less than 2% based on Formulation Development	Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge		Prior knowledge		Prior knowledge
Identification	Based on Control Strategy	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge	see 3.3	Water content unchanged after FBD	Water content unchanged after FBD	Water content unchanged after FBD
Microbiology	Specification of starting material		Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

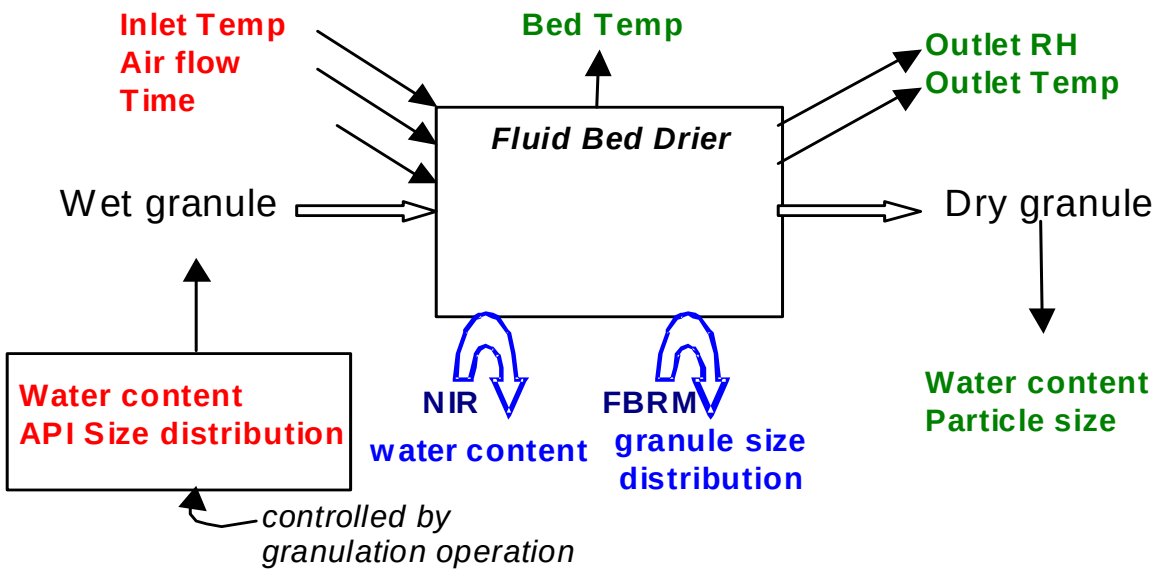
Fluid-bed Drying
Control Strategy

- Controlling both the final water content and the time course of achieving it (the “drying trajectory”), the performance of the examplain hydrochloride tablets can be assured

Control Strategy
Drying & Blending

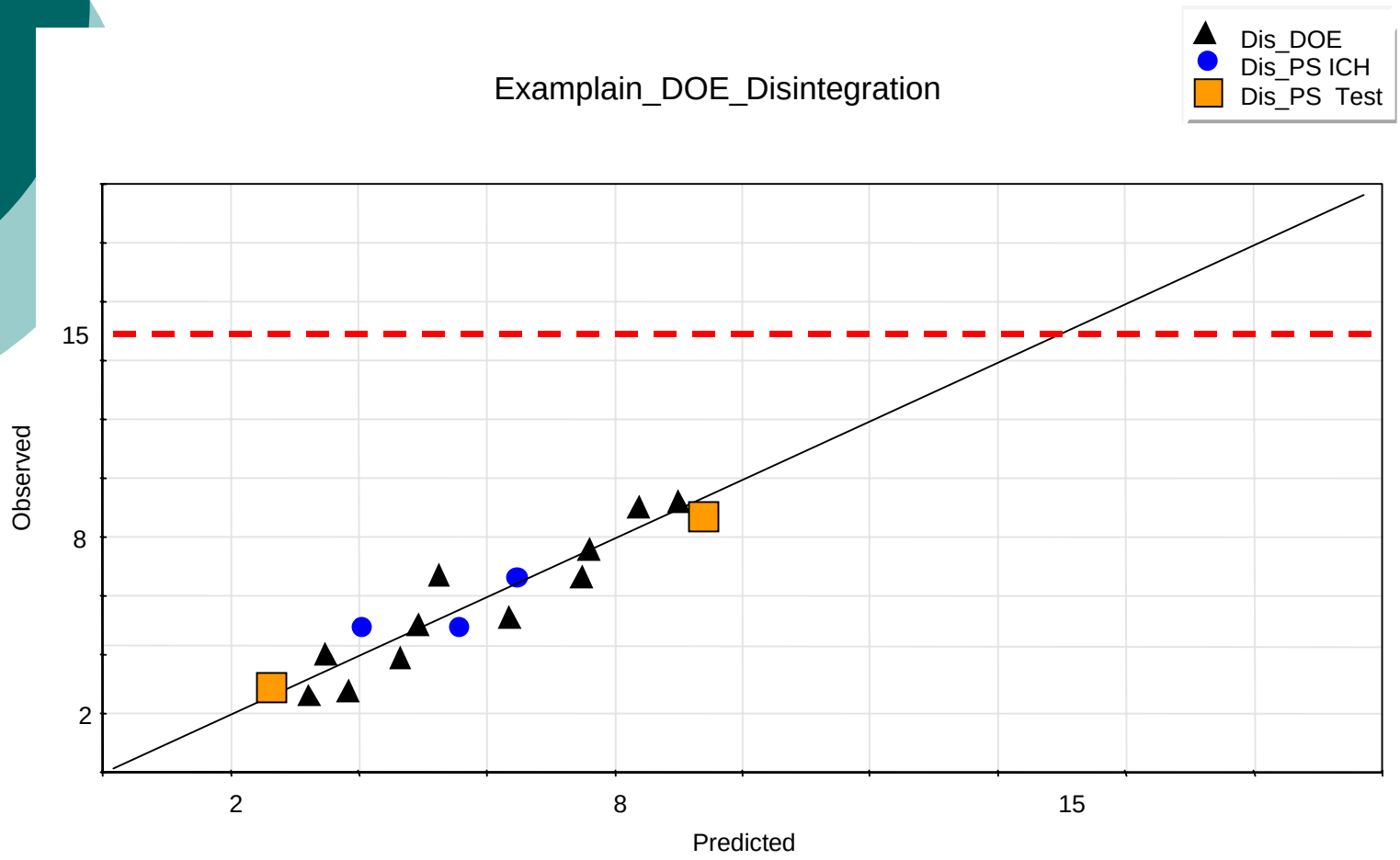
- The progress and end point of drying are monitored by on-line NIR and on-line laser particle size measurements
- The critical material attribute, water content of the granulate is controlled by adjusting air flow and inlet air temperature
- The particle size distribution is monitored by laser diffraction on-line measurements
- The end point of the drying is the range 1.5% to 2.0% water content with a target of 1.75% measured by on-line NIR
- The end point of the blending is determined by on-line NIR

Process Development
Key Process Variables for FBD



colour code: Red - input variables; Green - derived parameters; Blue - on-line measurements

A Multivariate Model for Predicting Disintegration



Scale:

- **Dis DOE**
- **Dis PS Confirmatory Batches**
- **Dis PS Test**

PS = Pilot scale

Control

- Process control strategy
- Product release strategy
  - RTR
  - Final product testing

Control Strategy 1/2

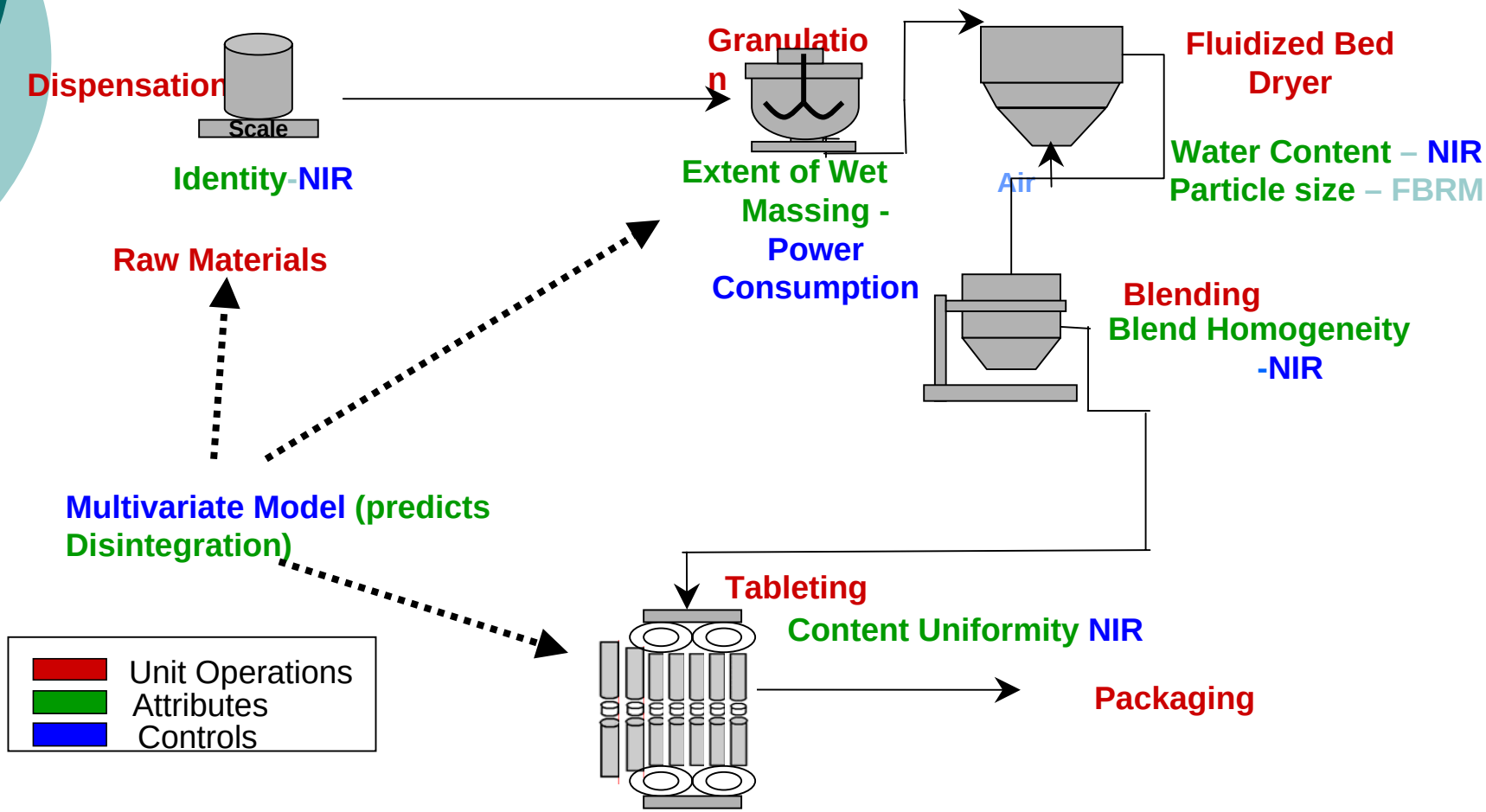
- Based on the Quality Risk Management the optimal control strategy is proposed so that all possible failures were reduced to an acceptable level
- Process controls including end point controls are established based on direct and timely measurements of relevant material attributes and relevant process parameters
- The control strategy proposed ensures that the natural variability of raw materials can be manage by the process itself
- The process therefore has been adjusted to give target quality endpoints of material attributes that are relevant for the next processing steps.

Control Strategy 2/2

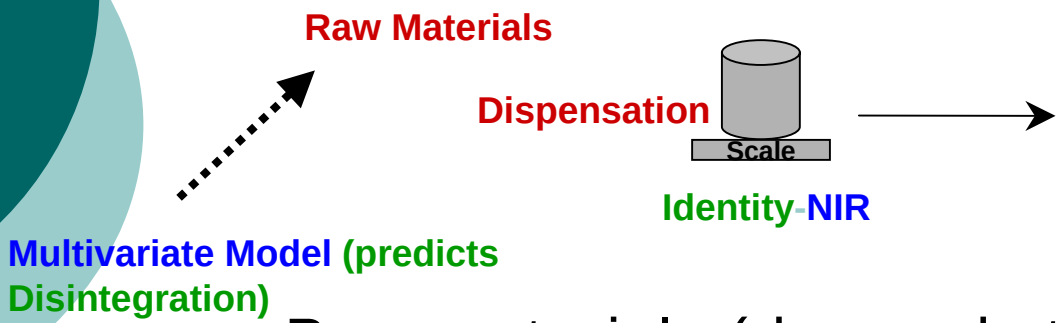
In summary the following process controls will ensure robust and consistent processes leading to consistent end product quality

- NIR for raw materials on receipt or when dispensing
- Power consumption for granulation end point
- On-line NIR and laser diffraction of the drying process
- On-line NIR for blend uniformity
- Compression force control and at-line NIR during compression for:
  - content uniformity
  - prediction of hardness
  - disintegration and dissolution

Manufacturing Process
- Control Strategy -

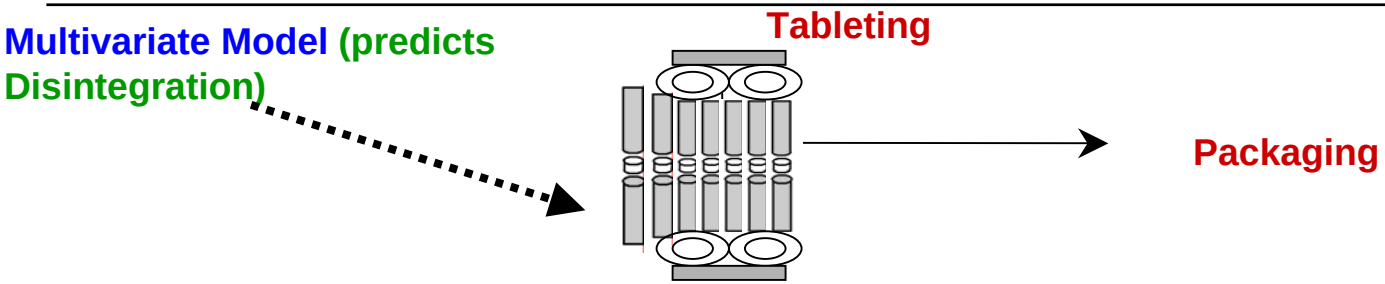


Control Strategy
Dispensing



- Raw materials (drug substance and excipients) identification are performed by NIR application
- The NIR spectra are also used to detect differences in physicochemical properties by correlating the NIR spectra in a multivariate way with end product quality characteristics
- Normal GMP double-checking of weighing and transfers assures correct weights of materials are added.

Control Strategy
Tableting



- Adjustment of the granulate feed through modern compression force feedback to control the process **ensures target tablet weight** and **consequently content uniformity**
- An automated weight control and at-line NIR measurement system allows feedback to the feed control and compression force system (compression of 100% tablets)
- At-line NIR confirms content uniformity and can detect any unexpected segregation of the blend during compression
- The NIR also allows the monitoring of water content of the final tablets
- A multivariate model for hardness, disintegration and dissolution allows prediction of hardness, disintegration and dissolution

Control Strategy 1/5
Impact on end product quality specification

Dissolution & Disintegration

- Mechanistic understanding of the disintegration and dissolution of *examplain* tablets
- Excellent understanding that no process or product formulation parameter within the established design space are critical for these quality attributes
- Established multivariate prediction model

Conclusion: Dissolution and disintegration of the final product will not be performed

Control Strategy 2/5
Impact on end product quality specification

Hardness

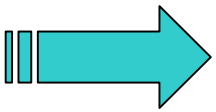
- Hardness is mainly influenced by wet granulation and compression force
- Instrumented compression force feedback control
- DoE showed that disintegration not significantly influenced by the hardness of tablets
- Prediction of hardness based on the correlation of NIR measurements with conventional hardness m measurements

Conclusion: Hardness is not a CQA for the present tablets and will not be included in the drug product specification

Control Strategy 3/5
Impact on end product quality specification

Assay and Unit Dose Uniformity

- Mechanistic understanding of relevant unit operations and impact on variations on content uniformity and assay
- Extensive process controls and monitoring
- Adjustment of all unit operations to defined material attribute end points
- Defined drying trajectories to control fine particle quantities
- At-line monitoring of content uniformity by NIR and the weight measurements



lead to reproducible results of
assay and content uniformity

Conclusion: At-line NIR measurements are basis for release decisions
on content uniformity and assay (Mean value)

Control Strategy 4/5
Impact on end product quality specification

Degradation

Des-ethyl examplain content at time of manufacture is influenced by:

- water addition rate during granulation
- by the trajectory of the fluid bed drying process
- the water content in resultant tablets

- Hydrolysis is minimized through control of temperature and water content of the granulate
- Control of drying process (other unit of operations have no effect) influence on level of degradation

Conclusion: Neither moisture content nor degradation product levels will be tested in finished product

Control Strategy 5/5
Impact on end product quality specification

Stability

Content of des-ethyl examplain is related to moisture content of tablets at time of manufacture and the uptake during storage

- Based on this underpinning science of water uptake and degradation rates:
  - the selection of the packaging material
  - the control of storage of bulk product before packing
  - long term data on pilot batches
  - supported by long term testing of the first 3 production batches

Conclusion:Reduce confirmatory stability testing after changes of equipment, scale or site, or other changes (assessed RM) up to 3 months based on QRA.

Regulatory Flexibility

Based on:

- Mechanistic process understanding
- Consequent application of Risk Management
- Development and implementation of Design Space for each unit operation
- Derivation of the critical to control attributes

Regulatory flexibility is proposed for the following topics:

- Process validation
- Scale and equipment change
- Site changes
- Real time release

Regulatory Flexibility
Process validation

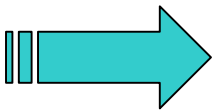
- Assurance is given that each process step (granulation and fluid-bed drying are examples) is routinely and reproducibly producing material for the next processing step through consequent manufacturing within established Design Spaces
  - Process verification in compliance with the design space
  - Application of the control strategy

Conclusion: Therefore the 3 batch validation will be replaced by a continuous process verification.

Regulatory Flexibility

Proposal for real time release

- Based on the high level of formulation and process understanding
- Extensive Quality Risk Management
- Sophisticated control strategy including advanced on-line and real time measurements of relevant material attributes



The consistent acceptable quality of the end product is guaranteed

No additional batch wise end product testing is needed.

Regulatory Flexibility

Scale & equipment changes

- Design spaces for fluid bed drying and wet granulation established
- These design spaces have been demonstrated to be transferable to and reproduced for different process equipment within the developmental work
- Different processing scales represented (1kg & 25kg)

Consequently the process will be operated within these design space

Conclusion:Changes of scale will be made immediately without notifying authorities

Regulatory Flexibility
Site changes

- Site change means reproducing Design Space at other sites:
  - with equivalent equipment
  - equivalent sources of raw materials
  - inspected GMP status of the site
  - with equivalent quality systems
- Conduction of full end product testing will be performed (first 3 batches)
  - Confirmation the validity of the process model
  - Confirmatory stability program for the first batches

Conclusion: Operation within developed design space, a transfer (site A to site B)could be made immediately without authorities being notified in advance

Discussion

Thank your for your attention