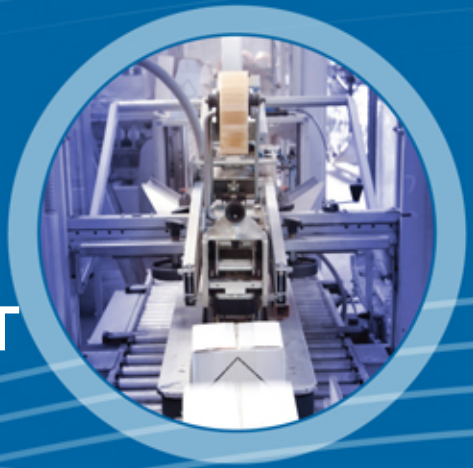
PDA Parenteral Drug Association

Connecting People, Science and Regulation

Case Study 3
Applying QbD for a legacy product and achieving real time release testing by a design space approach with supportive PAT and soft sensor based models: Challenges in the Implementations



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Joint Regulators/Industry QbD Workshop
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Case Study 3: team members

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Case Study 3: Overview

- Introduction to Case Study
  - Overview of the Product
  - Scope of the submission

- Discussion Topics

1. Assessing criticalities of process parameters / input variables and DoEs
2. Validation of Models supporting Real Time Release Testing (RTRT)
3. QbD in real life production

Overview of the product

- Indication: Chelation Therapy for the Management of chronic Iron Overload
- Drug Product: **Dispersible Tablet**
- Three Dosage Strengths with drug load 30 %
- Process Flow:

API

Charcoal treatment → Crystallization → Drying → Milling

DP

High Shear Wet Granulation → Drying → Blending → Compression

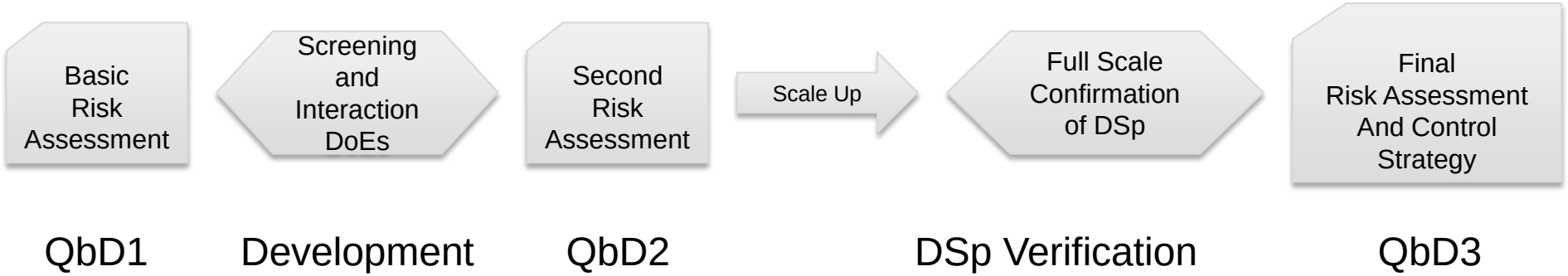
Introduction to Case Study

- Product N was initially submitted in 2005
- QbD pilot project was initiated 2006 for this legacy product and submitted in 2008/2009 as a variation comprising
  - The downstream steps of the API production (crystallization, drying and milling)
  - Complete Drug Product (DP) process
  - Introduction of new control strategy / RTRT elements such as
    - Design Space (DSp)
    - NIR for API Drying
    - NIR for Blend Uniformity (BU) and Content Uniformity (CU)
    - MSPC for some of the unit operations for process monitoring
- Pre-approval inspections took place for API and DP

Discussion Topic 1: Assessing Criticalities and DoEs

1

- QbD Development assessing criticalities of Process Parameters (PP) and input variables
  - Baseline Risk Assessment: “QbD 1”
  - Screening and Interaction DoE at Lab and Pilot Phase
  - Second Risk Assessment and Definition of Design Space (DSp) after development: “QbD 2”
  - Full Scale Confirmation of DSp (legacy product !)
  - Final Risk Assessment and DSp Verification Report “QbD 3”



FMEA Metrics

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- Fishbone diagram per unit operation to structure process parameters
- A 5 level scale was used to rank the parameters to calculate the Risk Priority Number RPN = I x D x P
- Threshold was set to 16 (2.5 x 2.5 x 2.5)
- Any value above 16 was studied within a DoE
- Severity/Impact threshold as an additional requirement for including the parameter in the DoE
- Criticality is dependent on risk: PxI
- High Detectability **does not** mitigate criticality

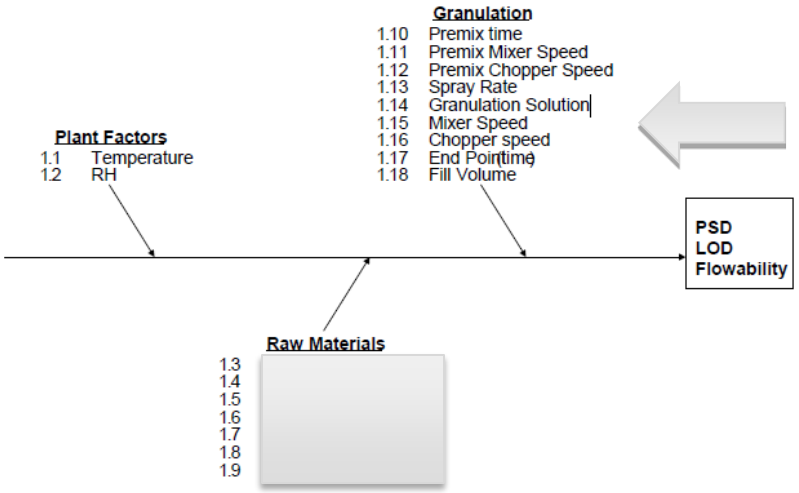
	Impact	Detectability	Probability
1	Negligible	Very high	Extremely unlikely
2	Marginal	High	Remote
3	Moderate	Moderate	Occasionally
4	Major	Low	Probable
5	Critical / Unknown	Very low	Frequent

Risk assessment

1

Example:
Water Amount
during Granulation

Figure 9-1 Granulation process fishbone diagram



No.	Name of Variable / Input	Current setting	Ref. No.	Potential Variability of Setting	P	(Potential) Impact on Output Quality	I	Detection in current process	D	Comment	RPN	DoE	Follow up, Control / Mitigation strategy
1.13	Spray rate		2b	Equipment failure	4	Flowability, PSD	2	Pump calibration	4		32	Y	DOE
1.14	Amount of granulation solution		1,2	Human error Equipment failure	3	Flowability, PSD, LOD	3	Double check of weight	2		18	Y	DOE
1.15	Mixer speed		6	Equipment failure	2	Flowability, PSD	4	Automated process	3		24	Y	DOE

Example of Screening Lab DoE

1

- 2^{5-1} fractional factorial design where each experimental variable was run at 2 level for a total of 16 factorial experiments with 4 target replicate runs

Table 2-1 Parameter ranges studied in the granulation DoE

Parameter	Lab scale ranges (Gral 25L)
Amount of granulation solution (ref. 1.14)	28 – 34%
Solution addition spray rate (ref. 1.13)	0.1 – 1.2 kg/min
Mixer speed (ref. 1.15)	Level 2 ± 10% 387 – 473 rpm
Fill volume (ref. 1.18)	4.00 – 5.50 kg
Endpoint (ref. 1.17)	1 – 4 min

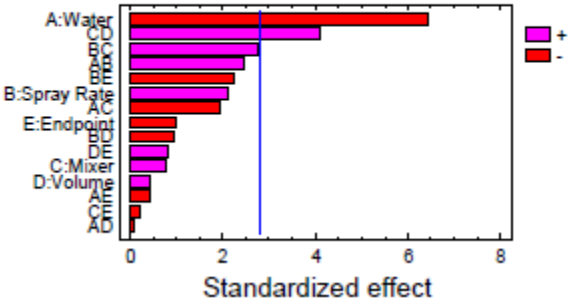
Table 3-1 List of batch numbers and corresponding experimental conditions

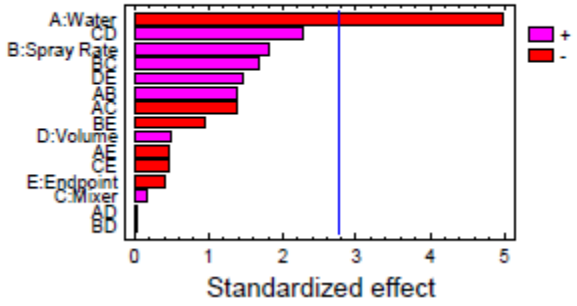
Run	Batch Number	Water amount (%)	Spray Rate (kg/min)	Mixer Speed (rpm)	Fill volume (kg)	Endpoint (min)
1	CRP136 0507	34.00	0,1	473	5,50	1
2	CRP137 0507	26.00	1,2	387	5,50	4
3	CRP138 0507	26.00	0,1	387	5,50	1
4	CRP139 0507	26.00	0,1	387	4,00	4
5	CRP140 0507	31.68	0,2	430	5,44	3
6	CRP141 0507	34.00	1,2	473	4,00	1
7	CRP142 0507	34.00	0,1	387	4,00	1
8	CRP143 0507	34.00	1,2	387	5,50	1
9	CRP144 0507	31.68	0,2	430	5,44	3
10	CRP145 0507	34.00	1,2	473	5,50	4
11	CRP146 0507	34.00	0,1	387	5,50	4
12	CRP147 0507	34.00	1,2	387	4,00	4
13	CRP148 0507	34.00	0,1	473	4,00	4
14	CRP149 0507	31.68	0,2	430	5,44	3
15	CRP150 0507	26.00	0,1	473	5,50	4
16	CRP151 0507	26.00	1,2	387	4,00	1
17	CRP152 0507	31.68	0,2	430	5,44	3
18	CRP153 0507	26.00	1,2	473	4,00	4
19	CRP154 0507	26.00	1,2	473	5,50	1
20	CRP155 0507	26.00	0,1	473	4,00	1

Risk Re-Assessment after DoEs

1

- Confirmed critical process parameter:
  Water amount during granulation



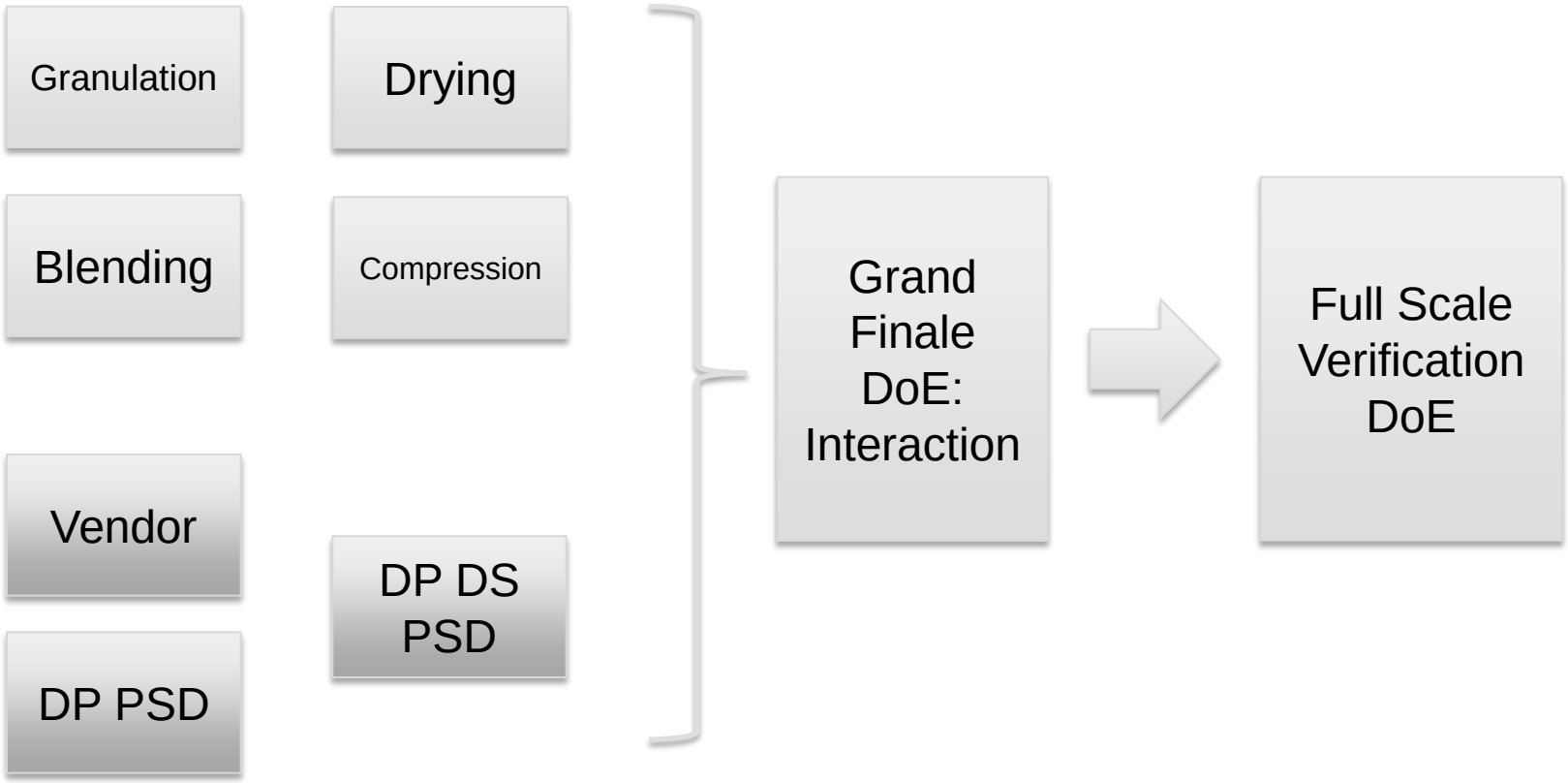


Assessment after DoEs

1.14	Amount of water	30%	1,2, 14, 15	Human error Equipment failure	2	Lower water amount increases dissolution rate and assay.	3	Automated process	2	Within the tested ranges of 22 – 34% an impact was found on dissolution rate and assay.	12	Equipment has been upgraded to allow control of the weight loss via a recipe.
1.15	Mixer speed	Level 2 (High)	6, 14, 39	Equipment failure	2	No impact on end product quality	1	Automated process	2	Within the tested ranges this parameter had no influence on the final DP properties on lab scale.	4	N	No mitigation strategy needed.

Flow of DoEs

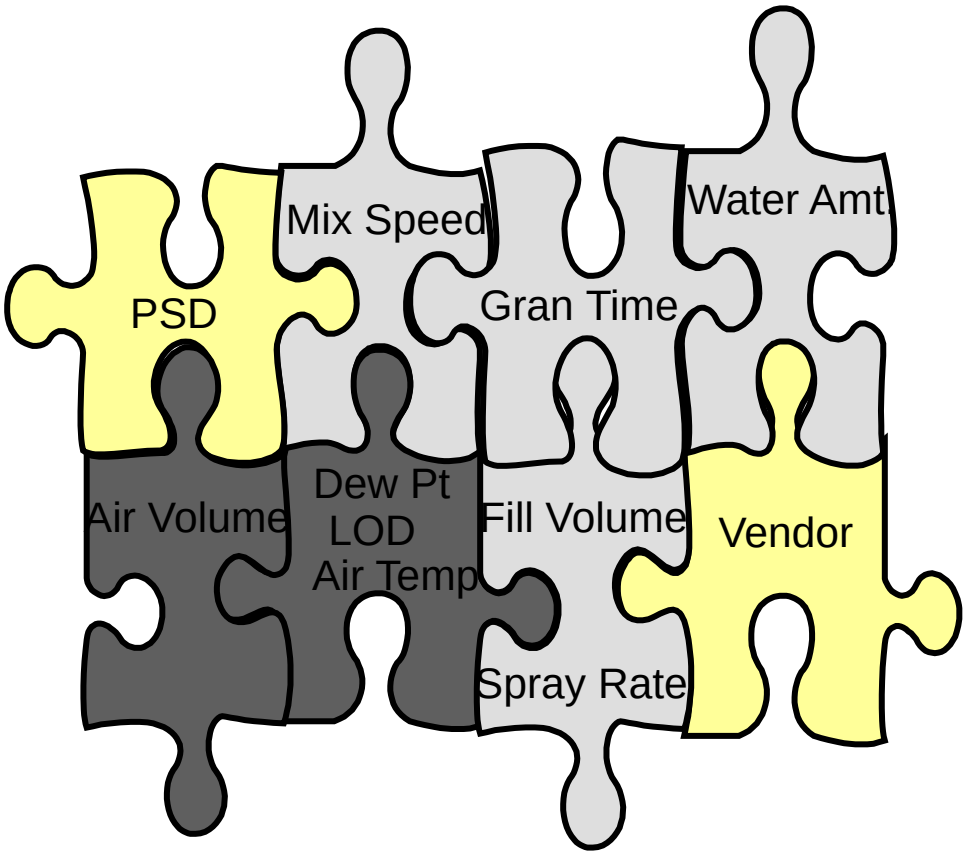
1



Main Effect & Optimization DoEs

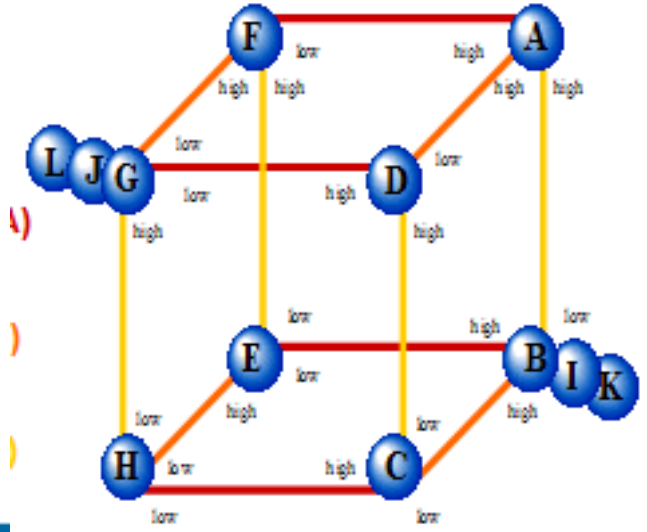
1

- Lab Scale Main Effect DoEs



- Lab Scale Optimization DoEs

- Full Scale Confirmation DoE



Discussion Topic 1: Assessing Criticalities and DoEs

1

- Observations / Learnings

- Fine analysis of the process (Fishbone diagrams) and clear RA methodology (FMEA metrics) driven by Severity.

- Outcome of DoEs: Only Pareto charts were presented.

  In this case study, no further focus on modelling:

  * DSp limits were not extreme

  * Although DSp was the surrogate for dissolution test at release, DP was a dispersible tablet (disintegration time < 3 min tested in-process).

  In principle, statistical results confirming the validity of the model are usually requested for DoEs establishing design space (goodness of fit, goodness of prediction, ANOVA p-values, …).

- Full scale DoE already executed: A protocol for DSp verification at commercial scale was not requested in this application.

Discussion Topic 1: Assessing Criticalities and DoEs

1

- Best Practice / Recommendations

- Level of details for review of RA depends on its use. If DSp claimed:
  * Comprehensive RA to understand the selection of variables in the DoE (individual scores and thresholds, with rationale)
  * Could be presented as risk matrix CPP vs CQA or as provided in this application

- Level of details for DoEs depends on the purpose:

  For screening, summary might be sufficient.

  For design space establishment, more details are needed:
  * type of experimental design
  * tables summarizing inputs (including batch size), ranges and results achieved for each experiment
  * if applicable, scale independent factors should be discussed
  * statistical significance of parameters studied with interpretation
  * summary of parameters that were kept constant during the DoE

Discussion Topic 1: Assessing Criticalities and DoEs

1

- Best Practice / Recommendations

- Use of commercial scale batches for DoE is not mandatory.

  Instead, a protocol for DSp verification at commercial scale is usually requested.

- Need for a clear and transparent Control Strategy: is a DSp claimed, or have PARs been investigated only for robustness purposes?

- A design space would normally include only CPP and CQA. Nevertheless, process description should include non CQA and non CPP.

- *Development of DSp* is detailed in CTD sections S.2.6 and P.2.

  Description of DSp should be presented in CTD sections S.2.2 and P.3.3.

  * Part of the regulatory commitments

  * Facilitates review by the assessor, indicating upfront the control strategy and the extent of flexibility claimed by the Applicant.

Discussion Topic 1: Assessing Criticalities and DoEs

1

- Best Practice / Recommendations

A satisfactory way to present the process description is in tabular format: one table for all the **target settings**, one table for CQA and CPP defining the **DSp with the corresponding ranges** (could also be a mathematical equation), and one table for **QA and PP not included in the DS** with their PAR.

Table 2-1 Target processing parameters for

Process step #	Parameter	Target value / range
1	Pre-mixing	Approx. 5 minutes
2	Granulation Solution Amount	
3	Fill Volume	
	Solution Addition Spray Rate	
	Mixer Speed	
	Chopper Speed	
	Granulation time	
4	Incoming Air Humidity	

Table 5-2 Manufacturing ranges for non-critical parameters for dispersible tablets

Variable	Quality Attribute (QA) or Process Parameter (PP)	Manufacturing range
Drug substance PSD	QA	
Lactose monohydrate 200 mesh PSD	QA	
Lactose monohydrate spray dried PSD	QA	
Fill volume (wet high shear granulator)	PP	
Solution addition spray rate (wet high shear granulator)	PP	

Table 5-1 tablets full scale Design Space

Variable	Critical Quality Attribute (CQA) or Critical Process Parameter (CPP)	Design Space Level Description
	CQA	
	CQA	
	CPP	
	CPP	
	CPP	

Tables' extracts from module 3.2.P.3.3

Discussion Topic 2: Models in the control strategy

2

- How to implement models supporting QbD control strategy
  - High, medium and low impact models
  - Validation of a model for CU
  - Validation of a model for BU
  - Usage of a MSPC Model
  - Level of details in the submission

Categories of Models

2

High impact model: sole indicator for quality and release

Examples in this application:

i. NIR for CU, drying (LOD) and ID

ii. Design Space model (dissolution)

Medium impact model: important in assuring quality of the product but not the sole indicator of product quality

Examples in this application:

i. MSPC for Granulation to assure normal operation conditions (borderline between levels medium and low)

ii. NIR for BU (borderline between high and medium)

Low impact model: support product and/or process development

Example in this application:

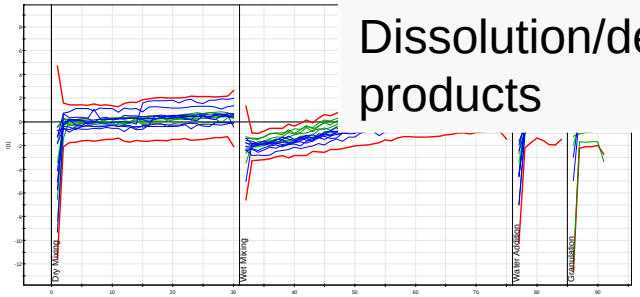
i. Main effect DoE

Control Strategy

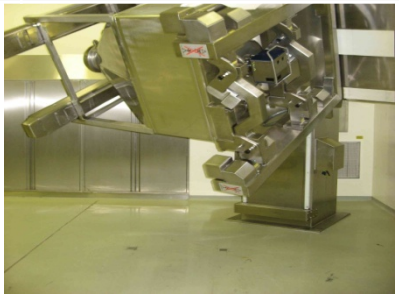
Granulation | Drying | Blending | Compression

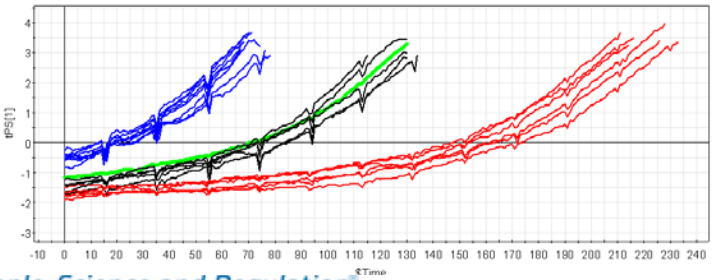
Test	Control Strategy
CU/ID/Assay	PAT
Dissolution/degradation products	Design Space

Uniformity



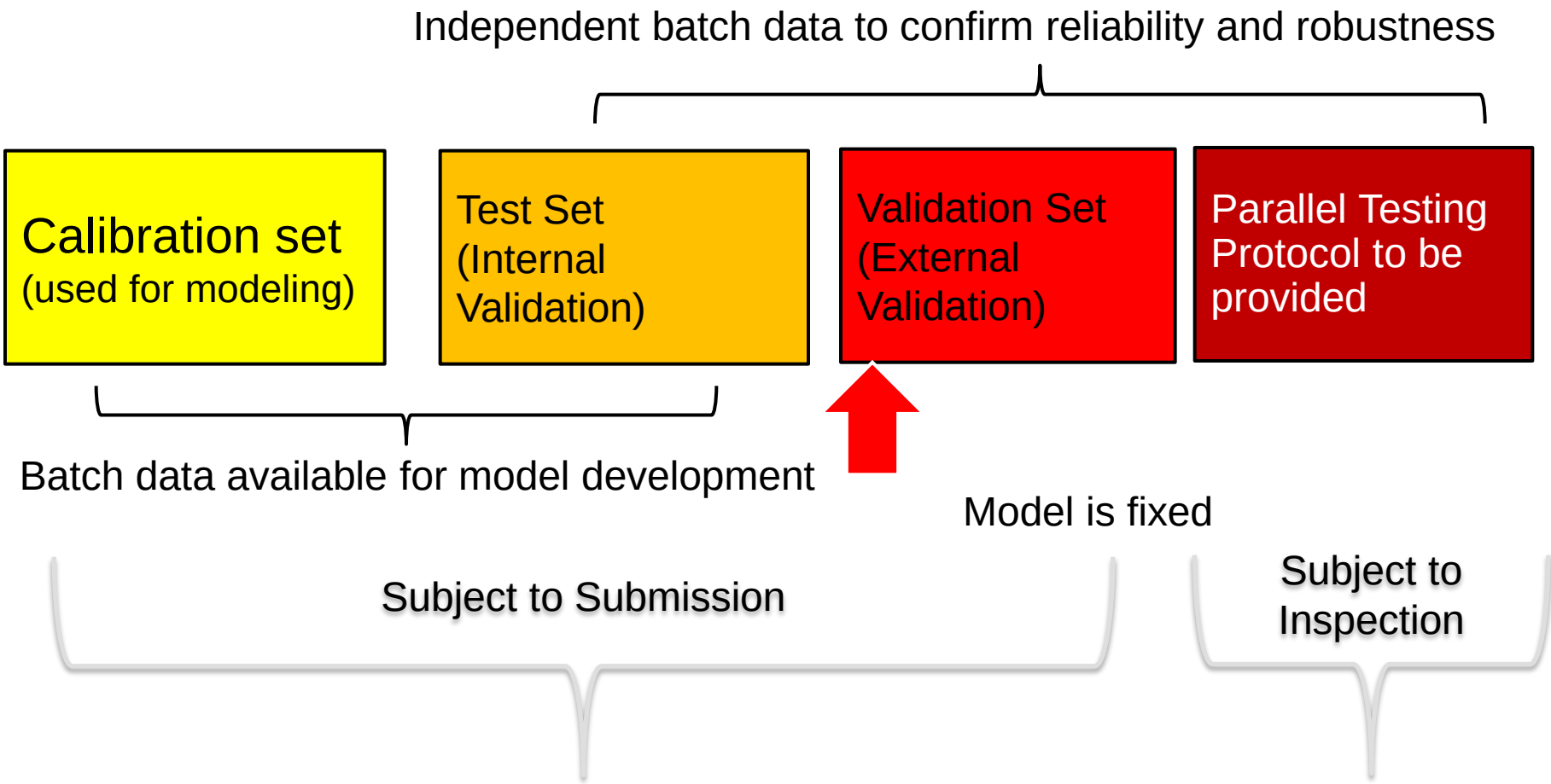
Models





High Impact models

2



Example CU by NIR

2

Development/Planning Scoping	Risk Assessment Calibration Design Feasibility Studies	→ Development Report
Data collection	Production and Measurement of Calibration Tablets (random design, 85-115 % of label claim) Definition of Acquisition Parameters	
Calibration Internal validation	Model Generation, optimization and finalization	→ Validation Protocol
External Validation	External Validation (n=3, punctual assessment) Method transfer on 3 batches Parallel Testing (statistical assessment n >> 3)	
Lifecycle management	Maintenance	

Risk assessment

2

- Robustness testing included
  - Excipients from different vendors
  - DoE batches (varying process conditions)
  - Hardness
  - Influence of Embossment, Operators and presentation of tablets

- Variability was incorporated by design or confirmed by testing
  - Random calibration design to avoid chance correlations
  - Inclusion of DoE target batches into the calibration

CU by NIR: Validation

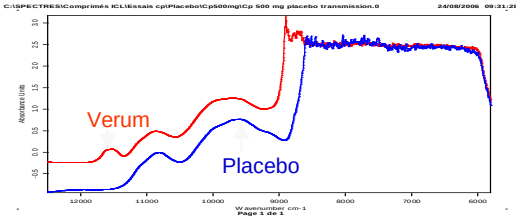
2

	Internal Validation	External Validation
	Assessment based **on a large number** of batches applying **statistical acceptance criteria** in a retrospective manner	**Punctual assessment** on a few individual batches (e.g. n=3) **with individual acceptance criteria** in a prospective manner
Accuracy	Bias, $SEP_{100batches}$ based on n=30 with low threshold: **Bias < 1 %**	Individual differences between model and reference with wider ranges $MAX_i \mid REF_i - NIR_i \mid < 3.5\%$ **Bias < 3.0 %** $SEP_{10tablets} < 3.5\ \%$

CU by NIR: Validation

2

Internal Validaiton	External Validation	Acceptance criteria
Linearity		Accuracy across the range Correlation coefficient SEC of calibration data
Specificity		Placebo tablets Specific aromatic overtone in the spectrum
Precision: Reproducibility		Six measurements with different operators



After validation the two methods are running in parallel for at least 15 batches (parallel prior to final implementation).

CU by NIR

2

- Observations
  - Weight correction not needed in this case as weight is tightly controlled and long experience/capability.
  - Range between 85 and 115 % because the model could not cope with a wider range (high drug load)
    * Generally 70-130% recommended to cover 2.9.40 requirements
    * In this case, reduced range justified by high dosage form, process capability and historical data on 200 batches.
  - Accuracy demonstrated across range on independent tablets but not on independent batches.
  - Not considered as real PAT since only 30 tablets were analyzed off-line.
  - Circumstances under which to go back to the old reference method clearly specified: NIR result outside of validated range, failure of NIR apparatus, investigation purposes.
  - No NIR raw data were requested only figures of the NIR spectra.

CU by NIR

2

- Learnings based on new guidance

  Concept of scope to facilitate continuous improvement and to manage how future changes to the procedure may be implemented from a regulatory perspective.

  Elements of the scope are detailed in the revised NIR guideline.

  For this case study, the scope was not clearly identified and some elements were missing for instance :

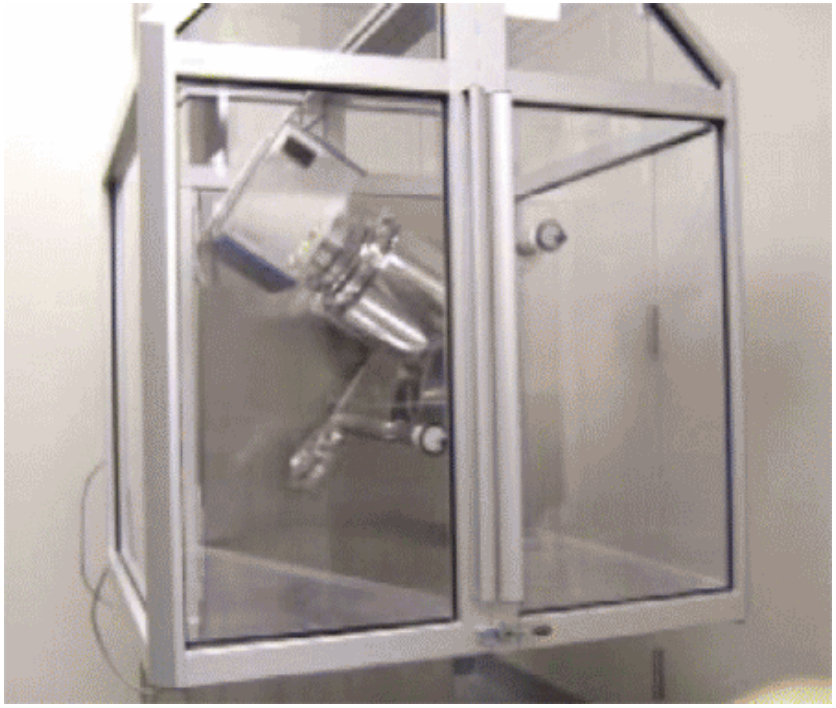
  - sampling interface model (drawing),
  - outlier detection mechanism (*e.g.* by Mahalanobis distance)

Topics for further discussion

Parallel testing: Number of batches (15) not a standard regulatory requirement (legacy product). However, protocol needs to be submitted and justified.

Example BU by NIR

2



- Quantitative Model was developed and validated at lab scale in the development center in NJ US
- Method was then transferred to the production site in CH

Implementation in Production

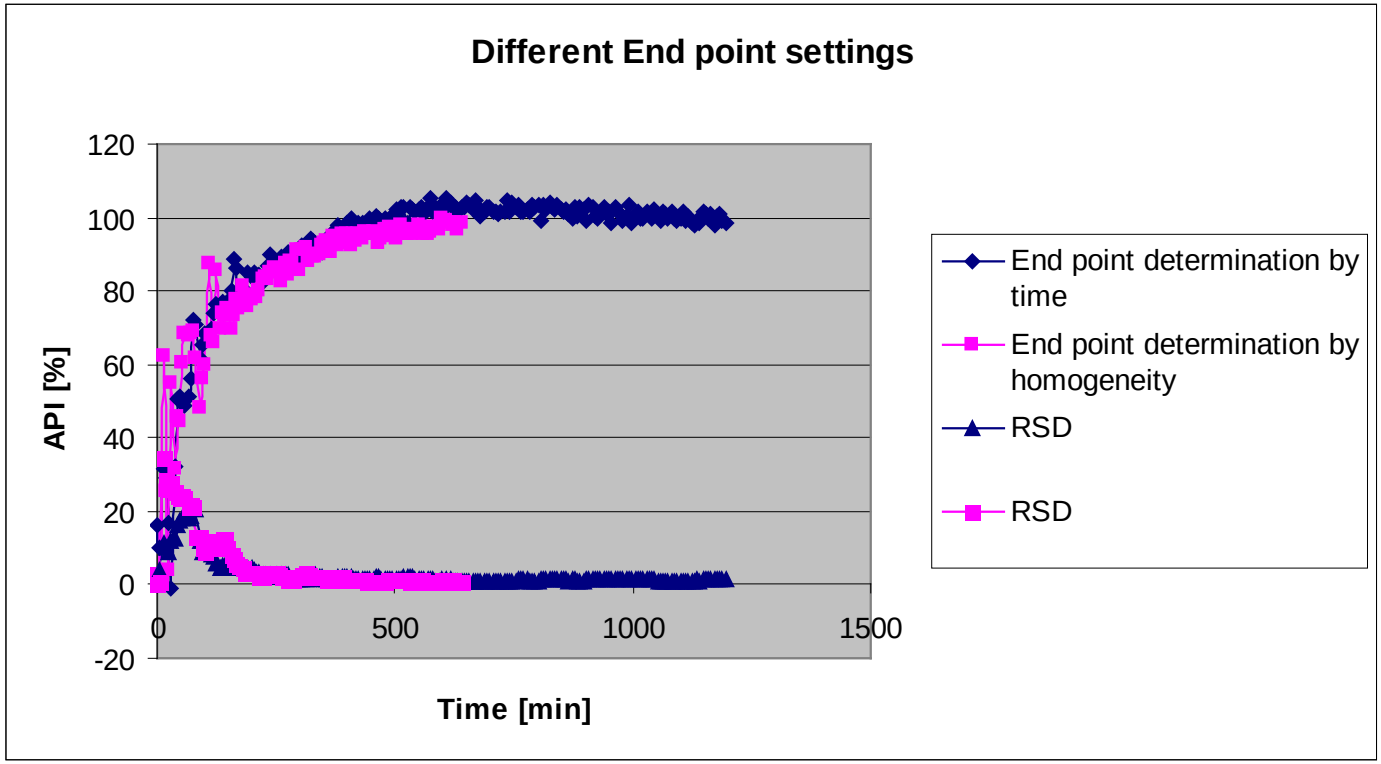
2

- Objective of the method
  - Online API prediction
  - Online moving block standard deviation of API prediction
  - Endpoint decision **not on time** but based on API concentration to be between 90 and 110 and standard deviation of API over the last 10 revolutions below 2.5

Validation for End Point Detection

Blending process is stopped based on NIR results

2



- The blending process is stopped when the defined endpoint criteria of the method are met.
- The blending time is shortened.

BU by NIR: Validation

2

- Built with external off line sample 70 - 130 %
- With this model the DoE batches with all variability could be monitored
- Robustness with rpm, fill level and PSD of API and excipients
- Transfer to full scale, comparability between lab and full scale
- Validation for on-line CONTROL by stopping a batch by the NIR signal and confirming with CU

BU by NIR

2

- Observations
  - BU by NIR considered a medium impact model since not used for release

Topics for further discussion

- In principle, requirements of the NIR guideline can be applied for the description and validation of BU quantitative methods.

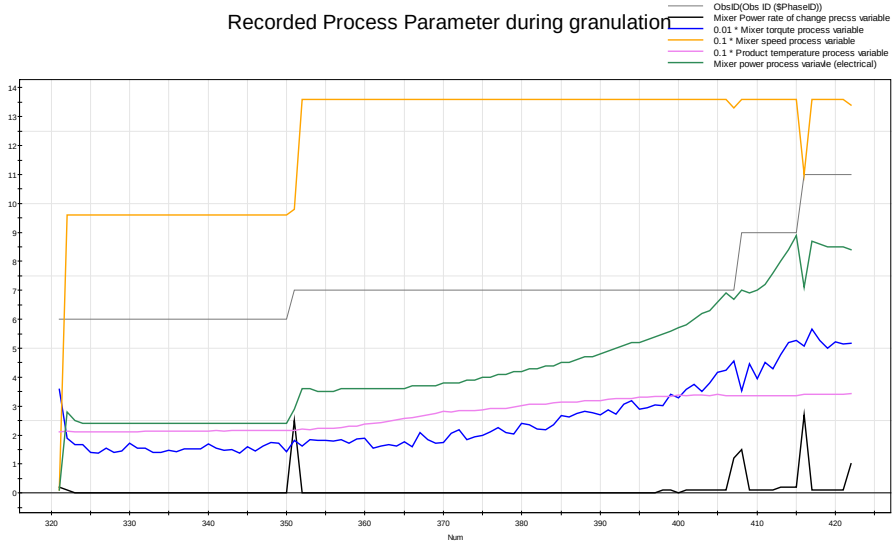
  It is up to the Applicant to justify his validation methodology.
- Sampling for the reference method:

  Complete replacement of thief sampling by testing of final tablets?
- Validation requirements for qualitative methods?

Multivariate Statistical Process Control (MSPC)

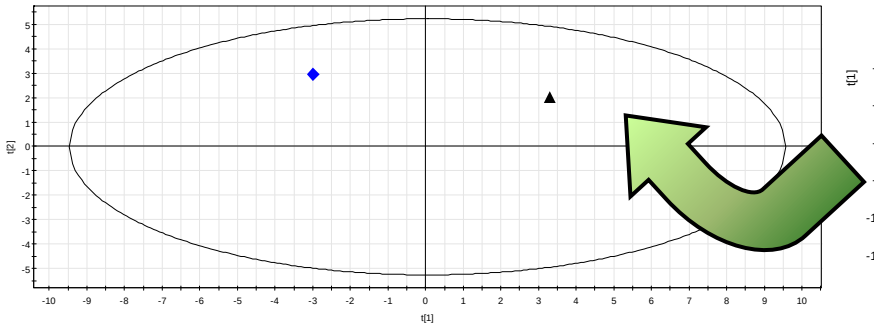
2

Recorded Process Parameter during granulation

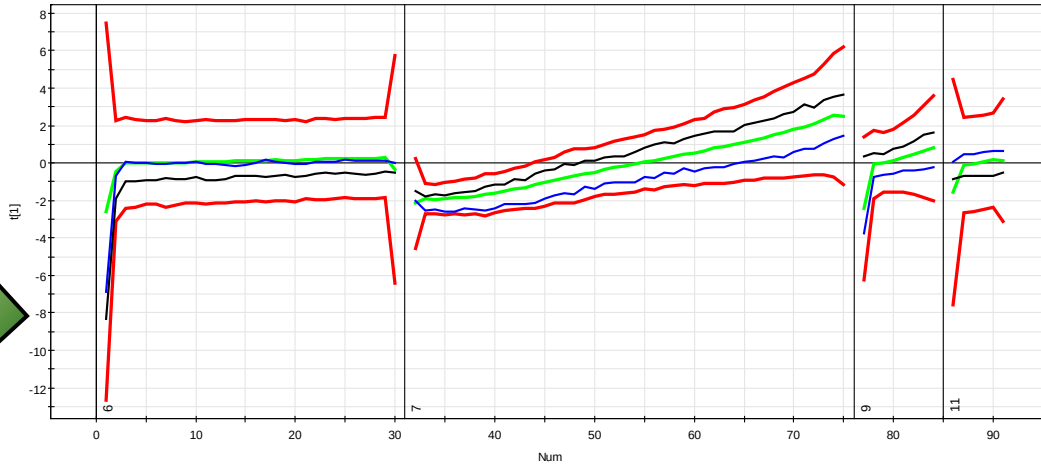


Process parameters are summarized in one quantity (process signature)

BSPC Analysis



SPC Analysis



MSPC for granulation and drying

2

- Learnings
  - Manufacturing process already validated (legacy product)
  - DSp verified at commercial scale
  - MSPC models (granulation, drying): part of a Continuous Process Verification to support continual improvement

MSPC models considered low impact

Consequence in terms of level of data requested

Validation data reviewed during inspection but submitted in the dossier for information

Discussion Topic 2: Models in the control strategy

2

- Best Practice / Recommendations
  - Level of details correlated to the impact of the model
  - Clear and transparent Control Strategy

    DSp as a basis for RTRT?

    PAT for release or for in-process monitoring?

    Monitoring for continuous improvement or alternative approach to validation?

    …

Discussion Topic 3: QbD Real life experience

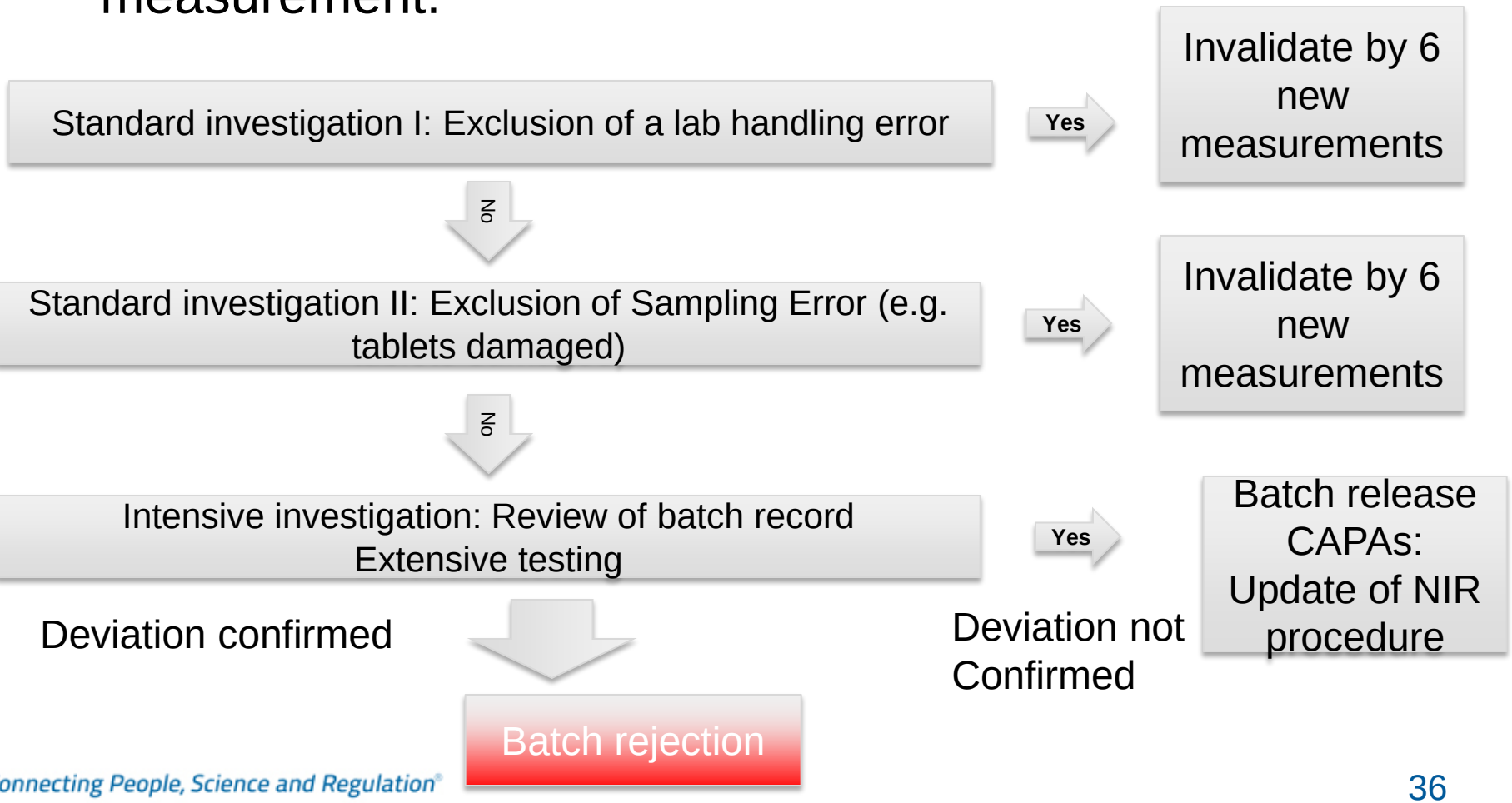
3

- Issues
  - How to handle OOS and OOE
    - OOS results from a NIR measurement
    - Excursion out of the Design Space
  - How to handle changes
    - High Impact models: Change of the NIR model
  - General expectations for a QbD Inspection
    - Pre Approval Inspection (PAI)
    - General GMP Inspection

Deviation Management for NIR

3

- Procedures following an OOS obtained by a NIR measurement:

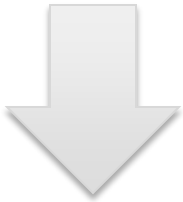


Deviation Management for DSp
Example

3

- Definition of DSp: Water amount at granulation 28 – 34 %

Incident: By a human error more water (35%) was transferred into the granulator



- Extent of deviation has to be evaluated
- Risk assessment (Impact on Quality)
- Evaluation whether process deviation can be handled by subsequent steps (drying)
- Scope of additional testing, e.g. IPC (LOD, PSD)?
- Full end product testing needs to be done

Deviation Management for DSp

3

Topic for further discussion

- Procedures following a DSp deviation:

Immediate action: Risk assessment and additional sampling whether to proceed

No → Severe deviation: Discharge batch

Yes ↓

Proceed with manufacturing with additional sampling if necessary

No ↓

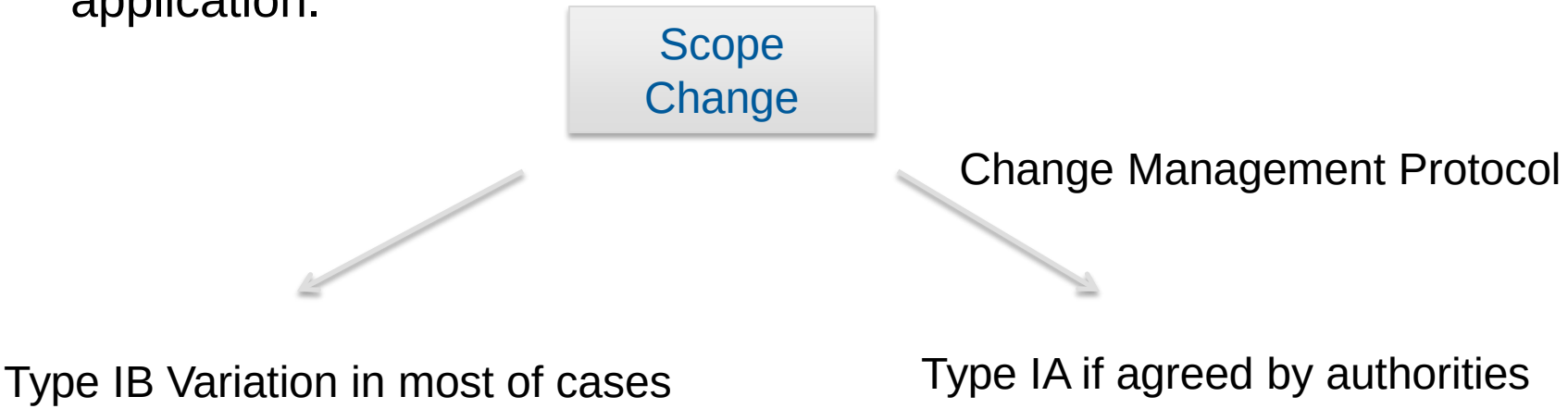
Full QC End Testing (no RTRT)
Thorough batch record review and risk assessment
Release decision based on the outcome.
OOS of DSp is invalidated by Risk assessment, additional data and full end testing

CAPA → Measure to avoid same incident
Tbd: Batch on stability
Extension of DSp with regulatory approval

Post approval change management

3

- Scope of a NIR procedure defines e.g. the instrument, substance to be tested, method characteristics, model...
- In daily life it is quite likely that the scope is changing, for instance new NIR spectrometer, update of model due to supplier change...
- Post-approval requirements for NIR procedures are covered by Section 7 of the latest revision of the NfG on the use of NIR. Changes outside the approved scope are subject to variation application.



Post approval change management

3

- Change Management Protocol:
  - Describes specific anticipated changes that a company would like to implement during the lifecycle of the product
  - Faster and predictable implementation of changes post-approval
  - Strategy and test procedure are agreed with Regulatory Authorities

- Examples:
  - Update of a spectral library for identification
  - Update of a quantitative method due to changes in the process (excipient vendor)
  - Update of the chemometric software for the predictions

Expectations for QbD Inspection

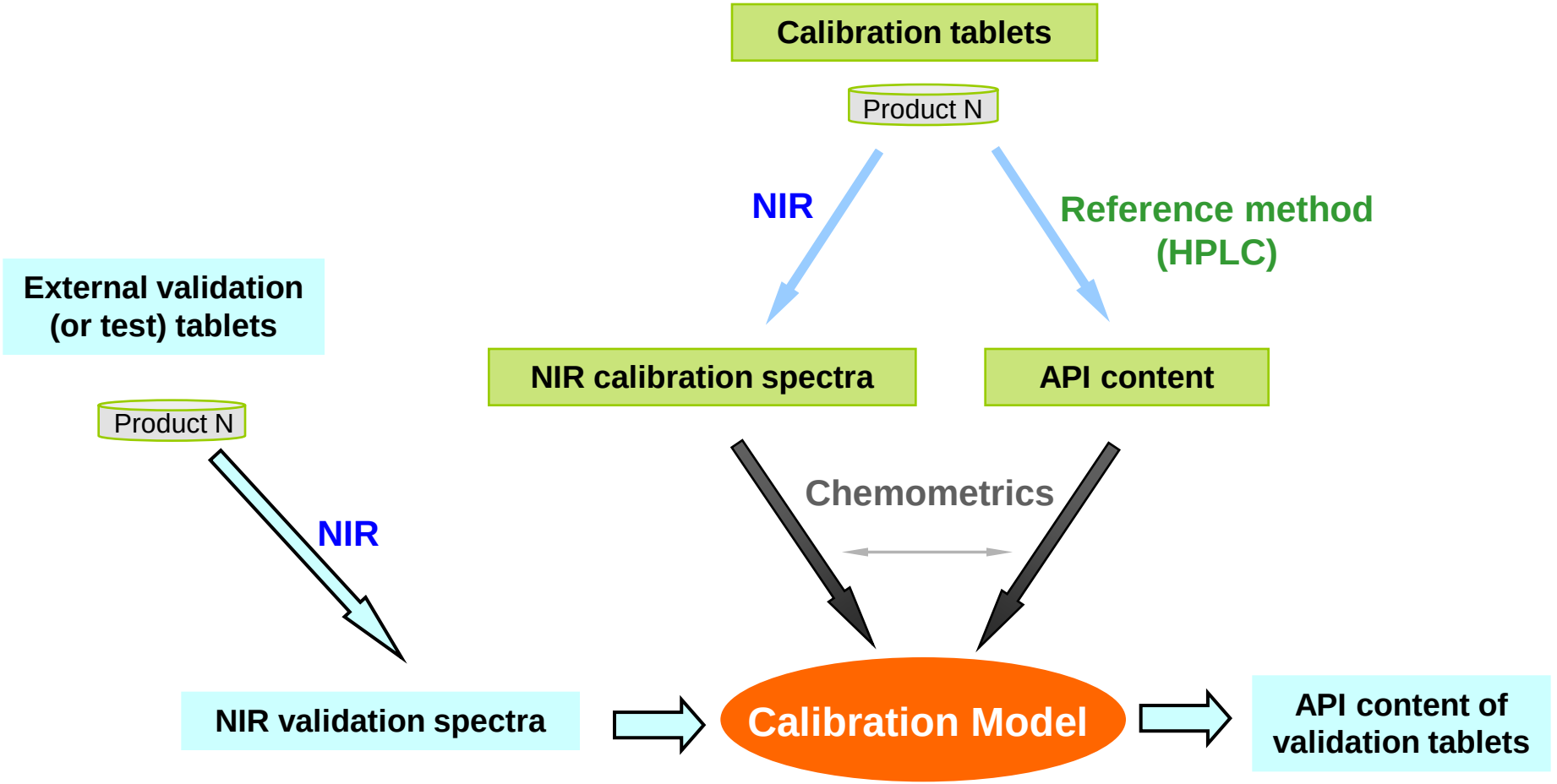
3

- Pre Approval Inspections (PAI)
  - Qualification procedures for PAT systems: URS, IQ,OQ
  - Qualification of automation and IT infrastructure: CSV, transfer of data, interfaces between sensors and data storage systems
  - Maintenance procedures
  - Periodic re-qualification
  - System SOPs (OOS, Change management,...)
  - Education/training records
  - Exchange with the assessor before and after the inspections
  - Ideally assessor would take part in PAI
- General GMP Inspection
  - Method performance as part of PQR and CPV
  - Deviations and changes
  - Results from parallel testing
  - Batch release procedures
  - Procedure for identification, evaluation and implementation of continuous improvement

- Background

CU NIR Methodology

2



Concentration distribution of randomized design

2

- Minimized concentration correlation between the API and principal excipients