Connecting People, Science and Regulation

Case Study 4: Challenges in the Implementation of Model Based and PAT based RTRT for a new Product

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The TEAM

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Case Study Main Points

- **RTRT as part of the control strategy for multiple CQA's**
  - **Description**
  - **Identification and Content**
  - **Drug-related impurities**
  - **Uniformity of dosage**
  - **Dissolution**

- **End Point Detection supports / integrates into RTRT**
  - **Granulation**
  - **Drying**
  - **Blending**

- **Design Space Across Unit Operations at Commercial Scale**

- **Lifecycle Support Considerations**

Overview of Product: Drug AA Tablets

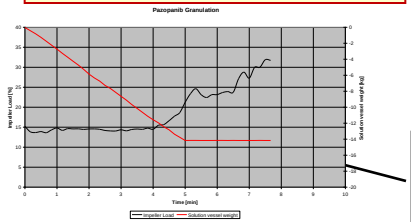
- Drug AA Drug Substance
  - Four stage manufacturing process with particle size reduction by micronization
  - Drug substance present as the hydrochloride salt (BCS Class II)
  - Submission contains enhanced product development approach

- Drug AA Tablets
  - Film-coated immediate release tablet for oral administration
  - 200 mg and 400 mg strengths; conventional wet granulation process
  - High Drug Content (66%) in the Tablets
  - Submission contains:
    - ✓ enhanced product development approach
    - ✓ control strategy based on comprehensive process understanding
    - ✓ real time assurance
    - ✓ proposal for real time release
    - ✓ process qualification and ongoing quality assessment using lifecycle validation approach

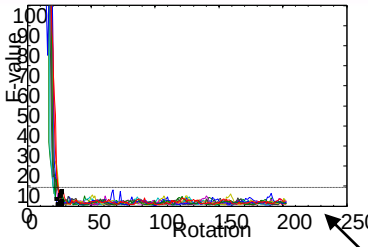
- Development and submission for this product preceded ICH Q8/Q9/Q10 implementation activities and uses terms that GSK subsequently updated to align with ICH QbD terms

Drug AA PAT within the control strategy

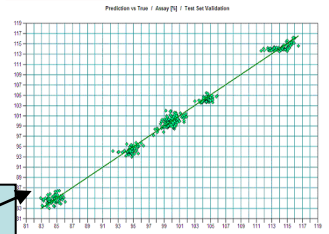
DCS Endpoint Control
IP21 data capture



NIR



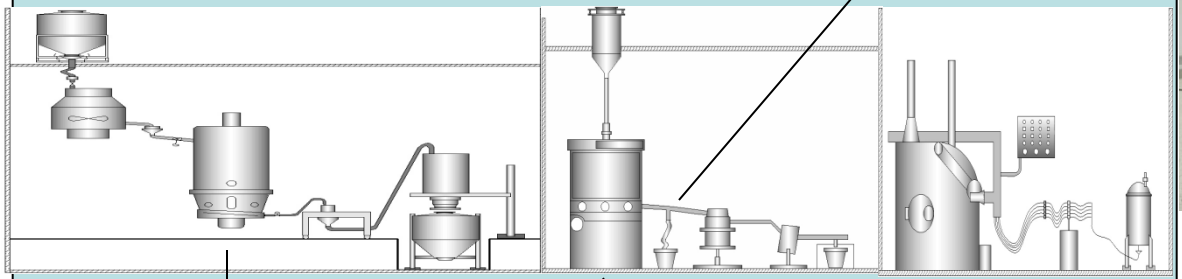
NIR



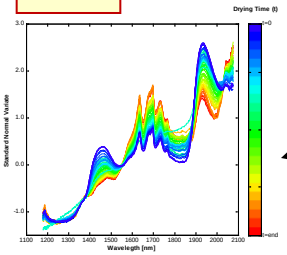
Granulation
Endpoint - Dissolution

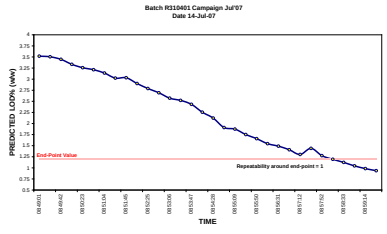
Blending
Homogeneity

Compression
NIR -Content & ID



NIR

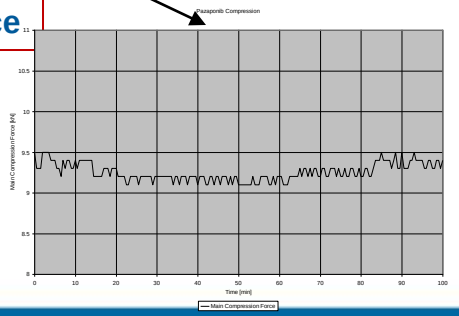




Drying
Moisture content

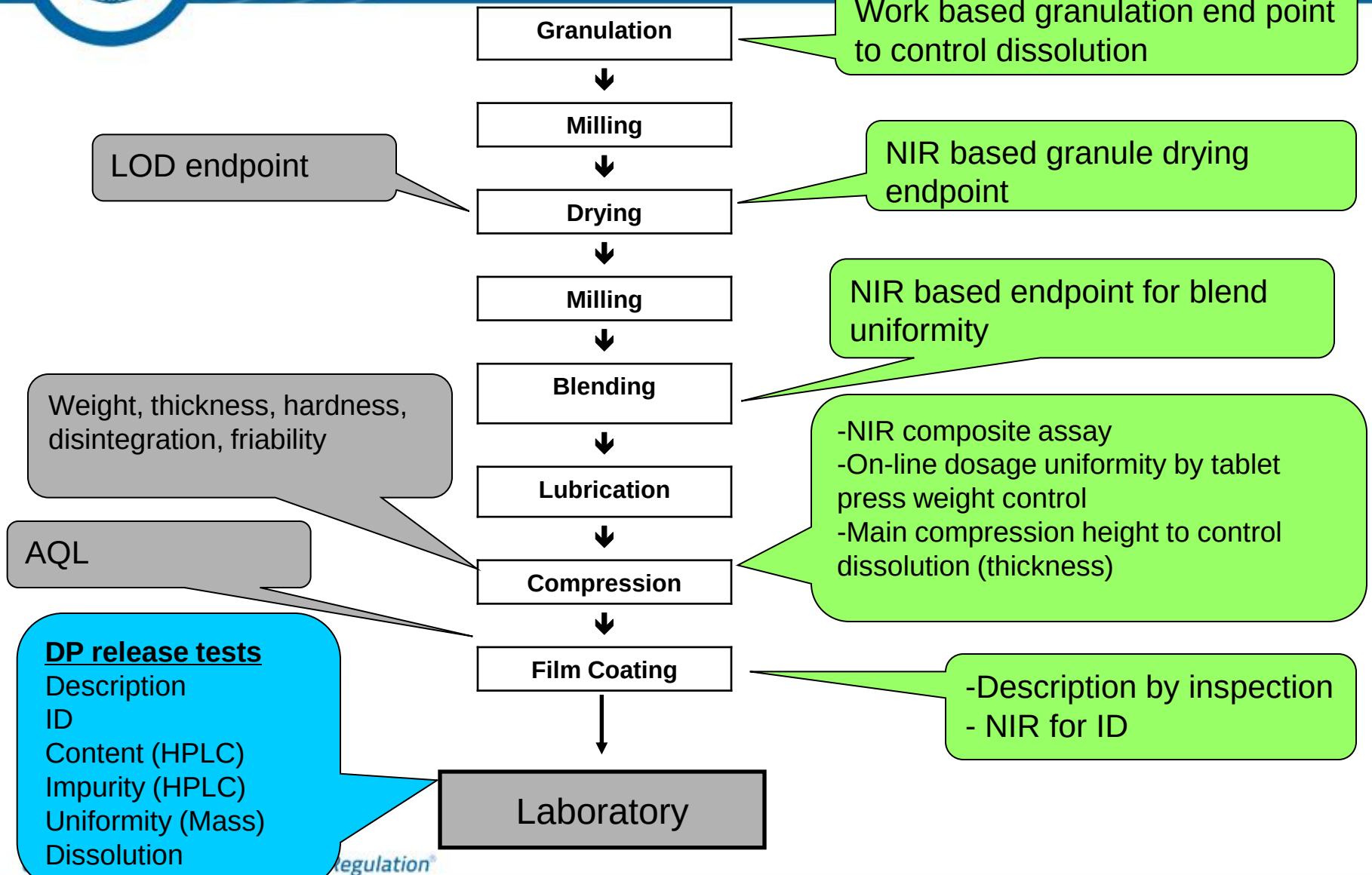
Compression
Main compression force for UDU
Thickness for dissolution

Compression Force



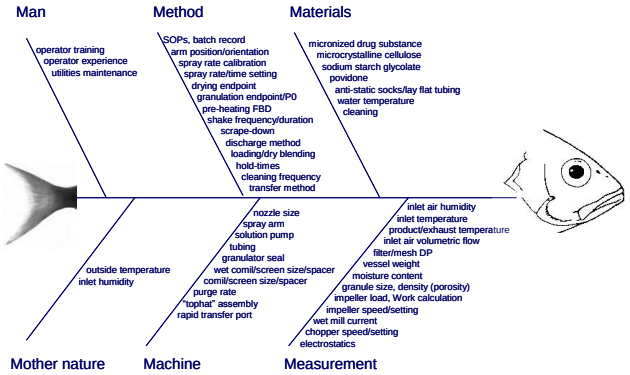
Traditional Release Approach

Proposed RTR Testing Approach

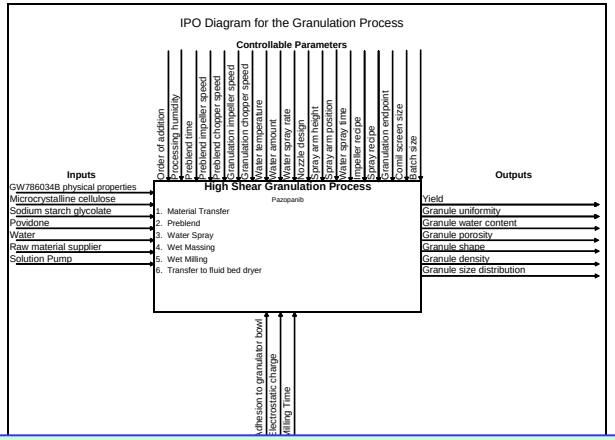


Risk Assessment was performed for All Unit Operations - Example Unit in this slide: Granulation -

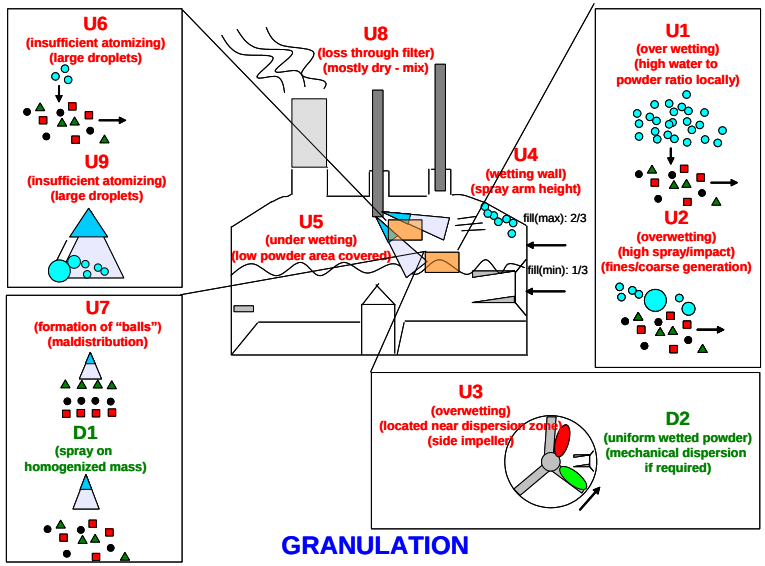
Fishbone/Ishikawa Diagram for the Granulation/Wet Milling/Drying/Dry Milling Process



IPO Diagram for Drug AA Granulation Process



Drug AA Granulation Transformation Flow Sheet Generated from BRITEST Review



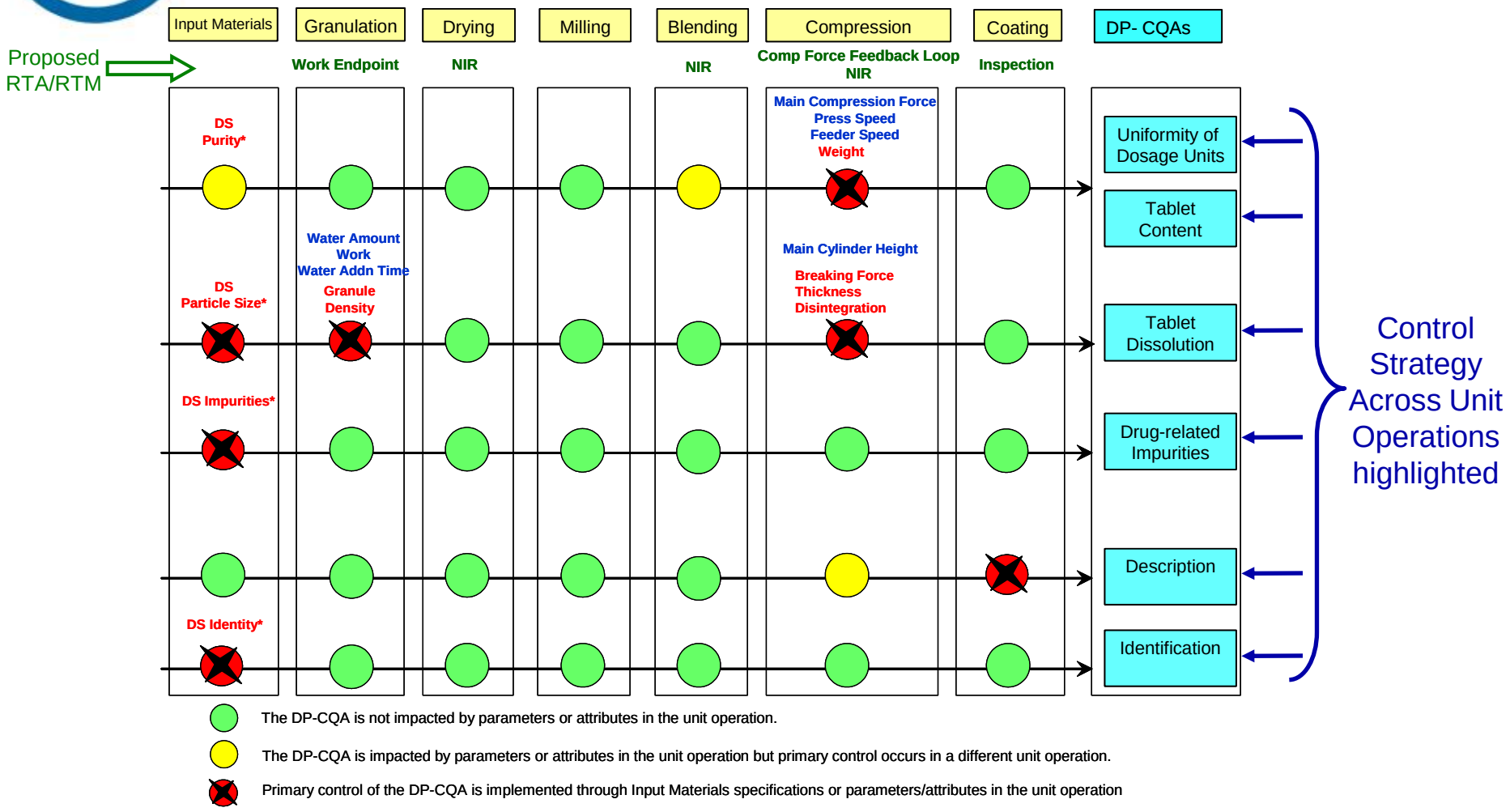
BRITEST performed on all Drug Product unit operations

Risk Assessments performed on all unit operations to justify decisions

Process Understanding and Control
Design of Experiments
(evaluated ranges were provided at submission, omitted here)

- **Granulation and Compression**
  - **Water Amount**
  - **Granulation End point**
  - **Tablet Thickness**
- **Compression**
  - **Press speed**
  - **Filomatic speed**
  - **Tablet Thickness**
- **Blending**
  - **Time**
- **Lubrication**
  - **Time**
- **Coating**
  - **Spray Rate**
  - **Inlet Air Temperature**
- **Micronization**
  - **Feed Rate (specific Energy model included)**

Drug Product Control Strategy



* Control of the Drug Substance CQA is described in m3.2.S.2

Model and Instrument based PAT

Soft Sensor : Granulation End Point

$$\text{Work} = \int_{0}^{\text{Time}} \left(\text{Power}_{\text{Impeller}} - P_0\right) dt$$

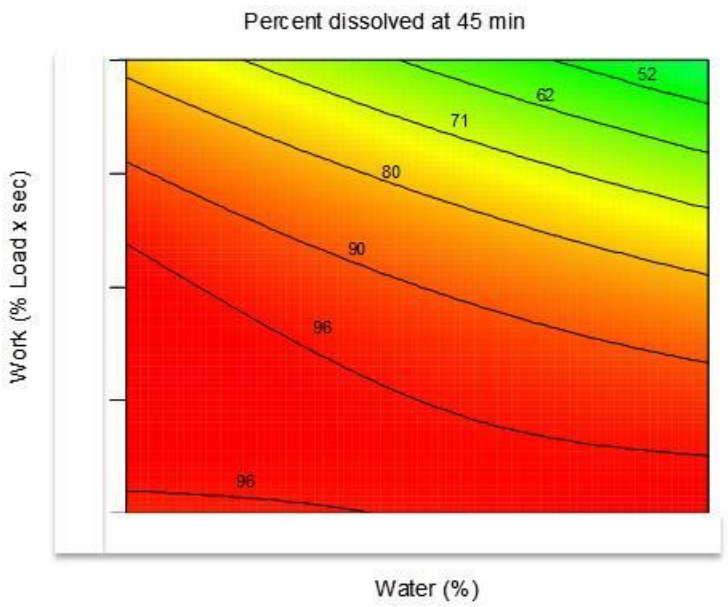
✓Granulation end Point is determined by amount of Work Input into Granulation.

✓Time-independent granulation endpoint approaches resulted in stronger correlations for models of dissolution and granulation attributes compared to the time-based approach of wet massing time.

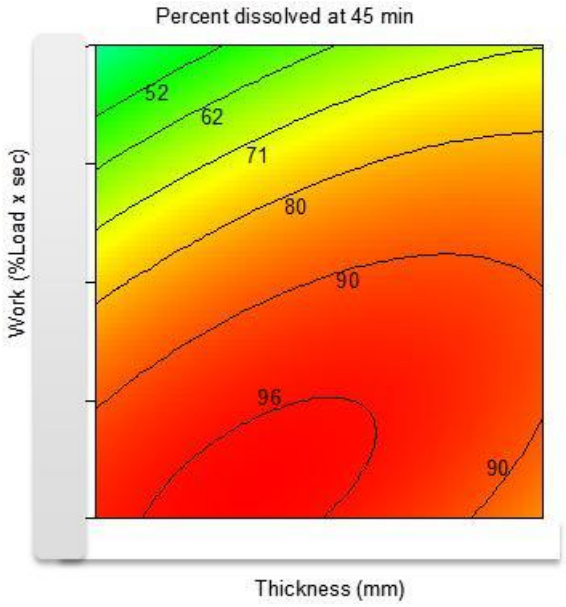
✓Controlled by DCS system

Dissolution DOE: Impact of Water Amount, Work and Tablet Thickness

Impact of Water Amount and Work (at Fixed Tablet Thickness of 6.55 mm) on Dissolution of Drug AA Tablets, 400 mg



Impact of Work and Tablet Thickness (at Fixed Water Amount of 30%) on Dissolution of Drug AA Tablets, 400 mg



Dissolution shows a strong correlation (R^2 = 0.92, p-value <0.0001) with water amount, Work, and tablet thickness.

Interactions & relationships presented in depth in the file

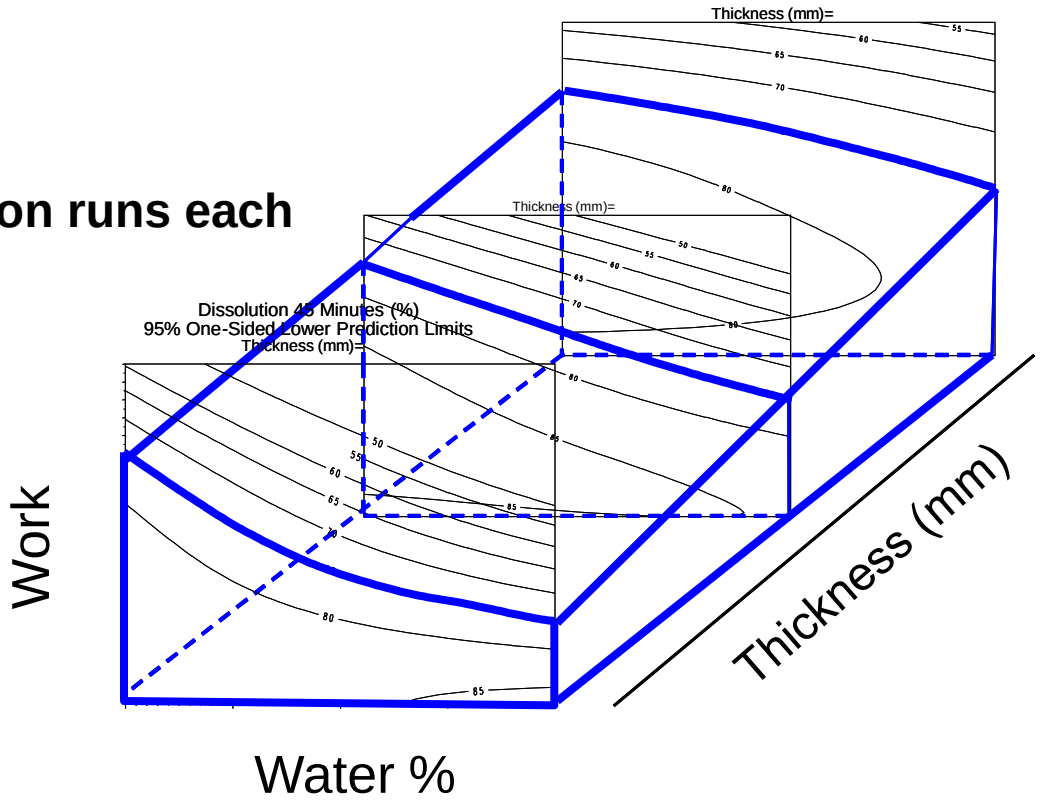
Design Space for Dissolution

DOE : 50 tablet batches (Commercial image)

Face centered central composite response surface
- 4 factorial, 4 axial, and 2 center points

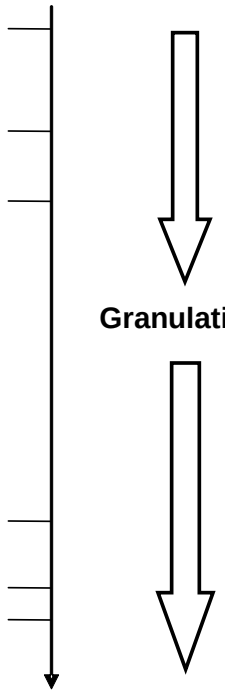
- ✓ **TEN granulation batches**
- ✓ **Commercial scale equipment**
- ✓ **subdivided to five compression runs each**

✓ Work based granulation endpoint provides stronger correlations compared to alternate time independent and time based granulation endpoint

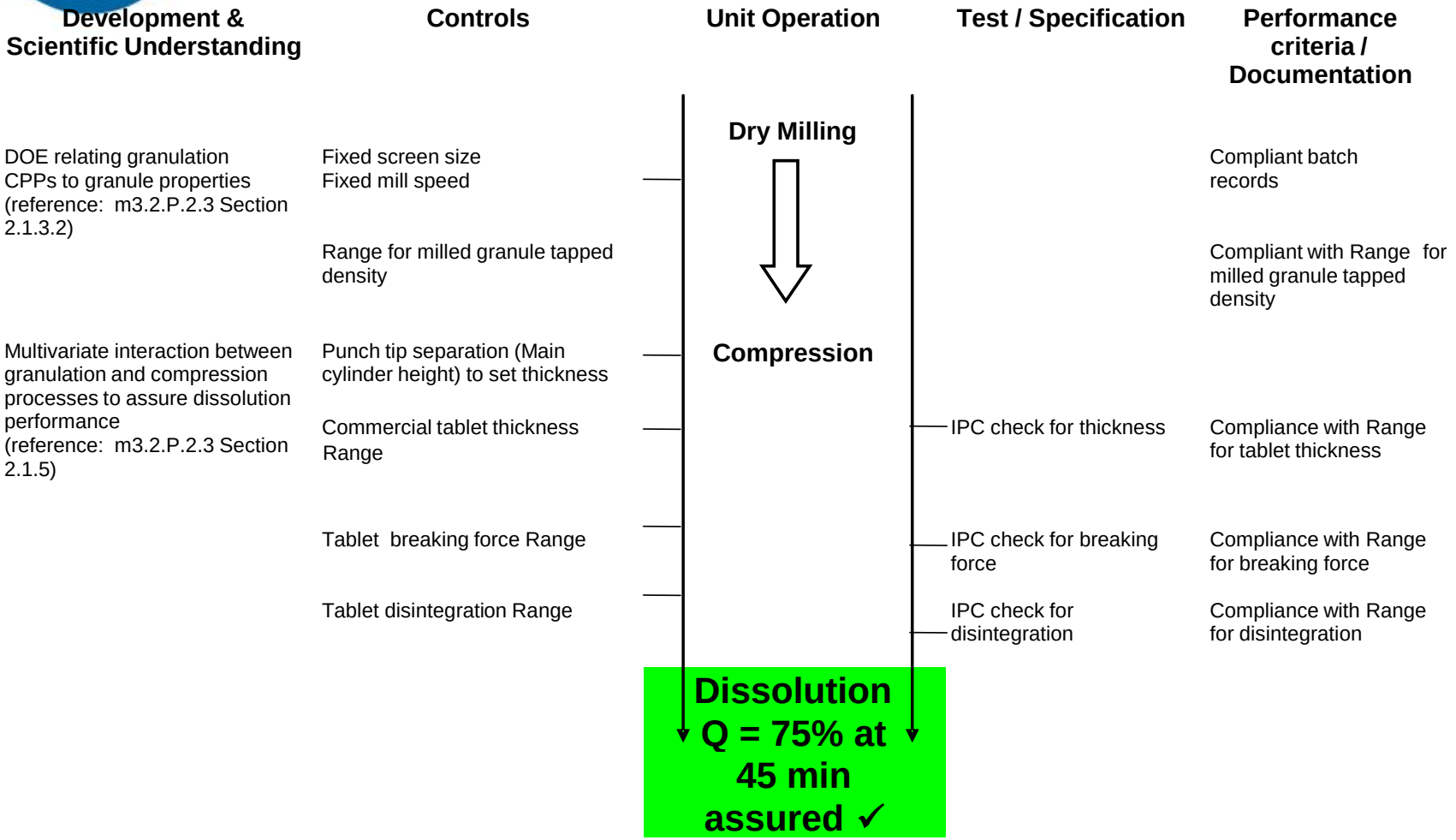


Control Strategy for Dissolution

Development & Scientific Understanding	Controls	Unit Operation	Test / Specification	Performance criteria / Documentation
		Dispensing		
Impact of drug substance particle size (reference: m3.2.P.2.3 Section 2.1.4.1)	Micronized drug substance particle size distribution (PSD)		Specification: X_{10}, X_{50}, and X_{90}	Compliant drug substance COA
Batch formulation (reference: m3.2.P.2.2 Section 1.2.2.3)	Drug substance purity		Specification for purity	Compliant drug substance COA
	Bill of Materials			Compliant batch dispensing record
Granulation endpoint (Work) and water amount based DOE specific to equipment and scale of manufacture (reference: m3.2.P.2.3 Section 2.1.3)	Fixed equipment	**Granulation**		Compliant batch records
Range for water amount, addition time, and Work (reference: m3.2.P.2.3 Section 2.1.5)	Range for water amount			Compliance with Range for water amount
	Range for Work and water addition time			Compliance with Range for Work and water addition time



Control Strategy for Dissolution (Continued)



Parallel Testing, Dissolution

- 30 batches chosen to evaluate process control and variability in input materials to provide adequate statistical power for control charts and setting meaningful control limits

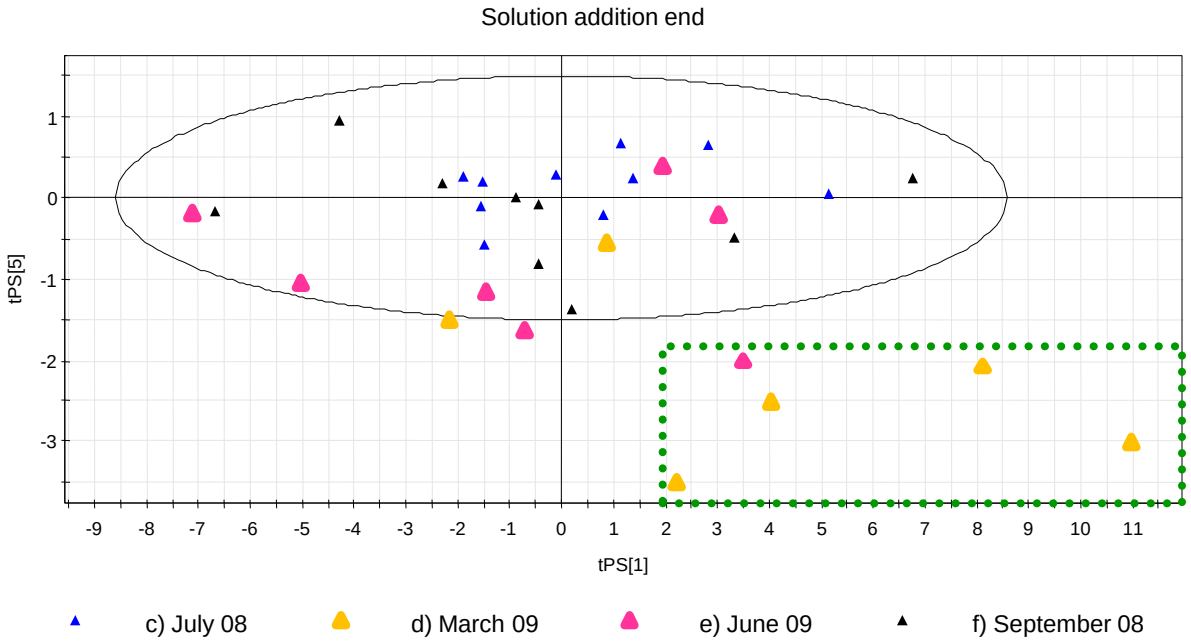
Acceptance Criteria

- Adherence to control strategy including compliance with CPPs and CQAs
- Each individual batch mean greater than 80% and average of 30 batches greater than 89% at 45 min and each batch complies with USP General Chapter <711>
- Conservative acceptance criteria at target water amount and Work (granulation endpoint) at 95% confidence and prediction intervals
- Actual dissolution to be compared to model prediction and confidence intervals (no predictions planned for each batch)

During PAI

• A comprehensive multivariate model was presented during PAI to support the dissolution design space and overall control strategy.

•This model together with the Design Space can support RTRT for Dissolution.

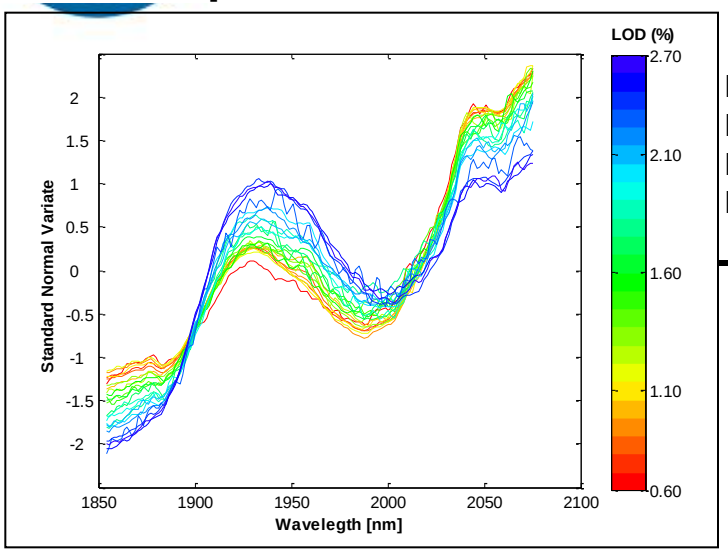


- Discussion

Near Infrared Technology and Implementation

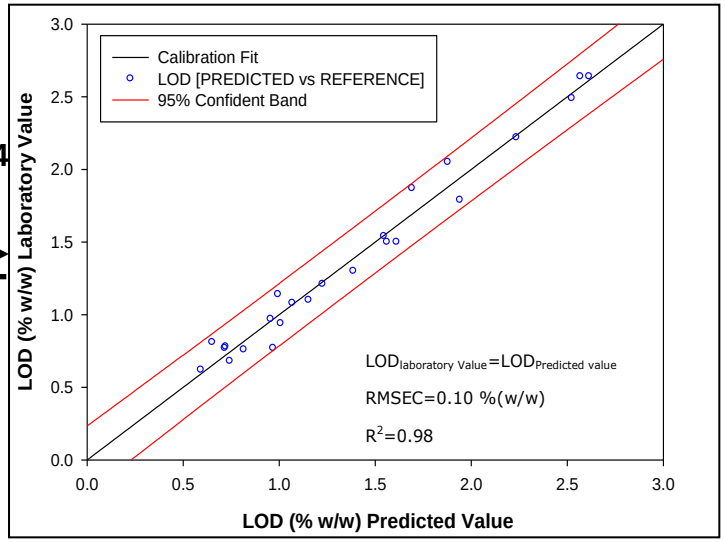
NIR Drying Model

NIR Spectra & LOD values

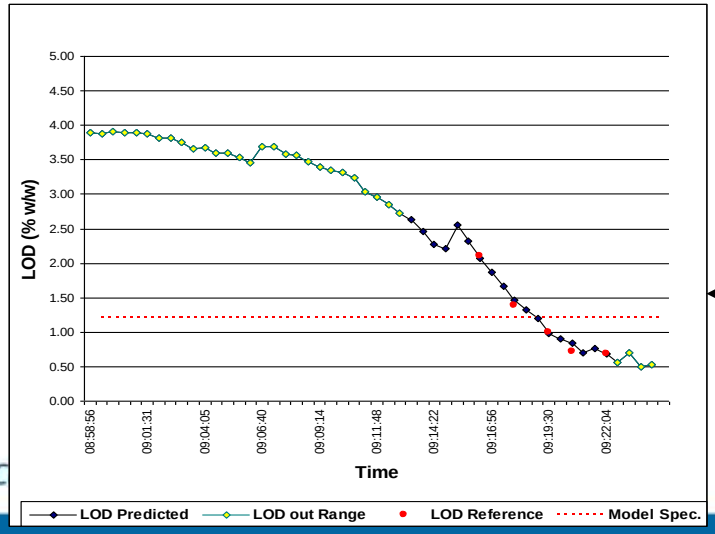


R=0.98
RMSEC=0.10
N° Samples =24
Factors=1

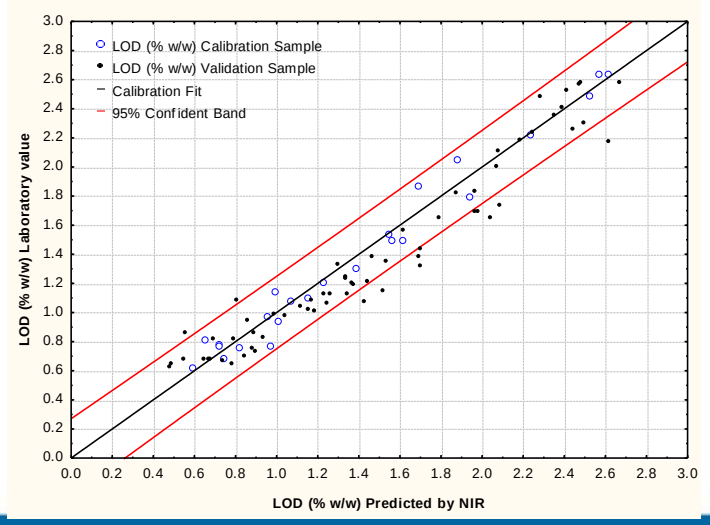
Calibration



Implementation

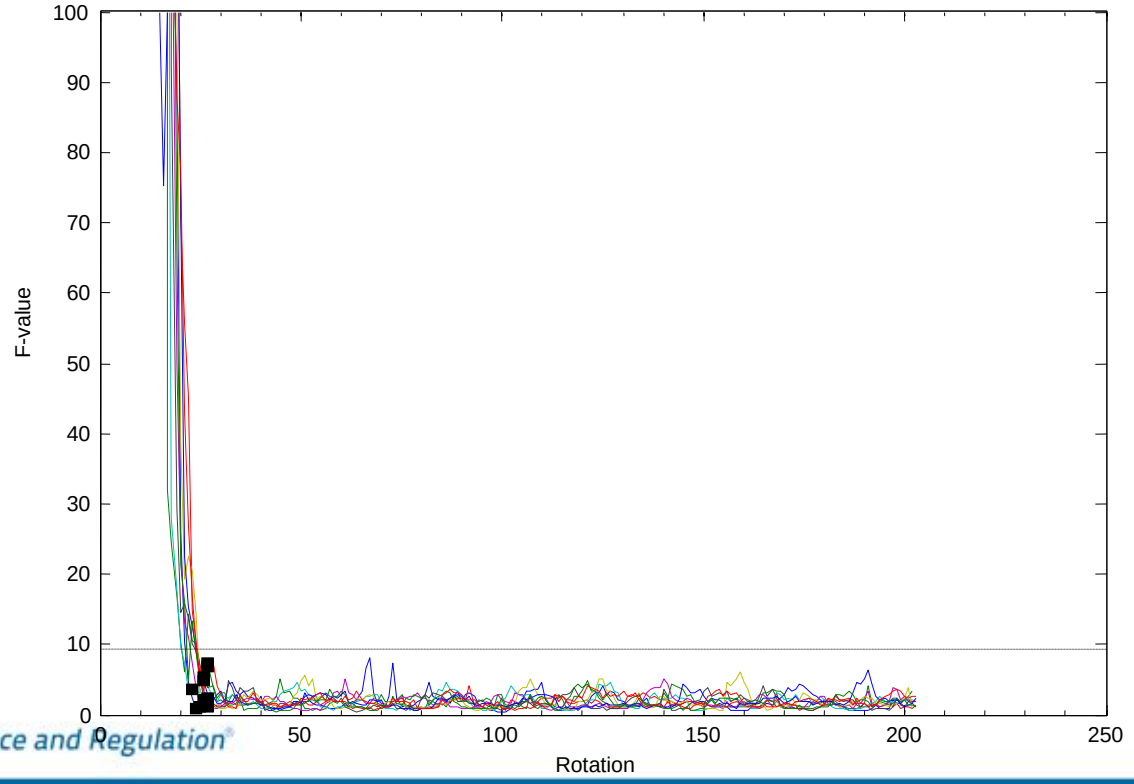


Validation



Blend homogeneity model

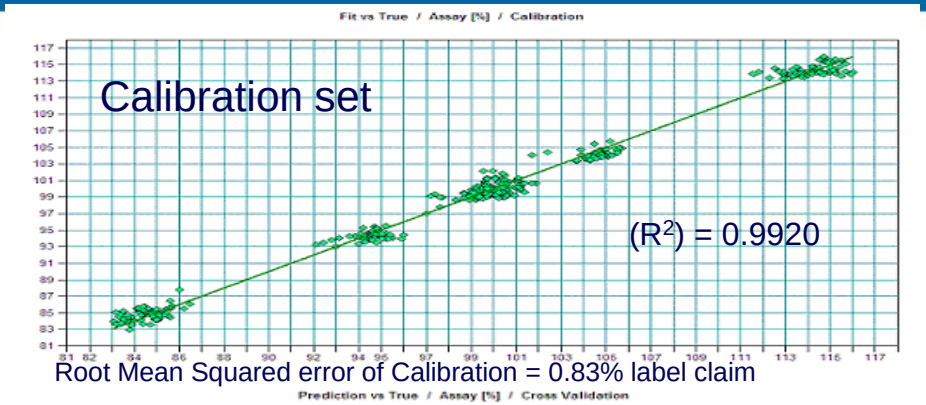
- The model does not require correlation with a primary reference method
- The Caterpillar algorithm provides an objective criteria for assessing variability (F Test)
- Requires knowledge of the mass of sample analysed (i.e. effective sample size)
- It uses only data collected during the blend of that batch to assure blend homogeneity.



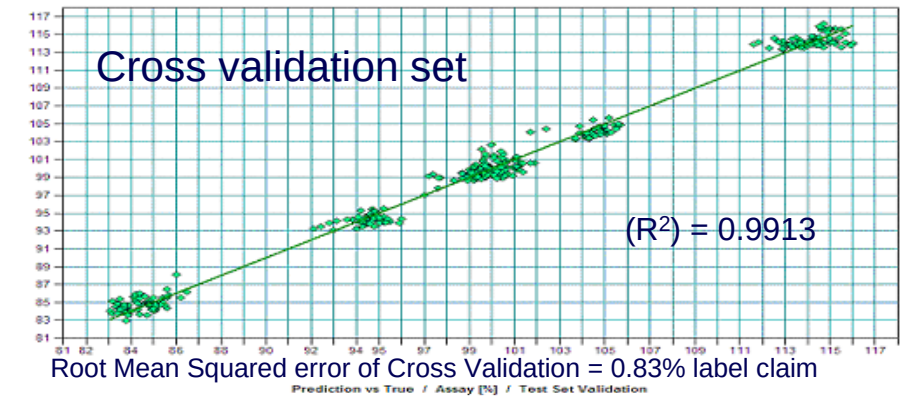
Content Model Development

Model Dataset

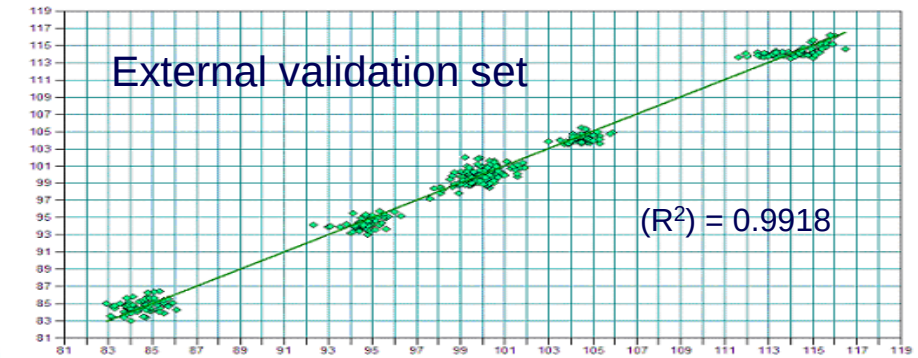
- Tablet shape (commercial image and clinical image)
- Dose strength (200mg and 400mg)
- Concentration (85 – 115% of nominal
- Weight (+/- 5% target)
  - 400mg
  - 200mg
- Thickness tested
  - 400mg clinical, a range
  - 400mg commercial, a range
  - 200mg clinical, a range
  - 200mg commercial, a range



Root Mean Squared error of Calibration = 0.83% label claim



Root Mean Squared error of Cross Validation = 0.83% label claim



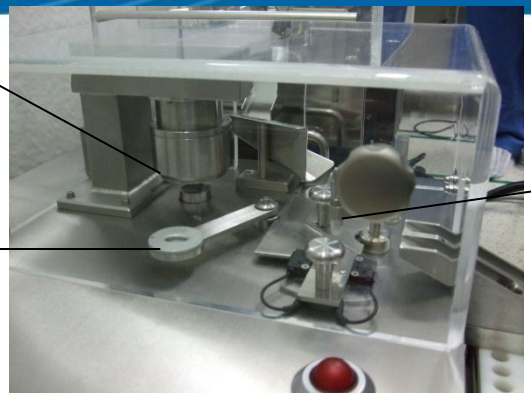
Root Mean Squared Error of Prediction = 0.83% label claim

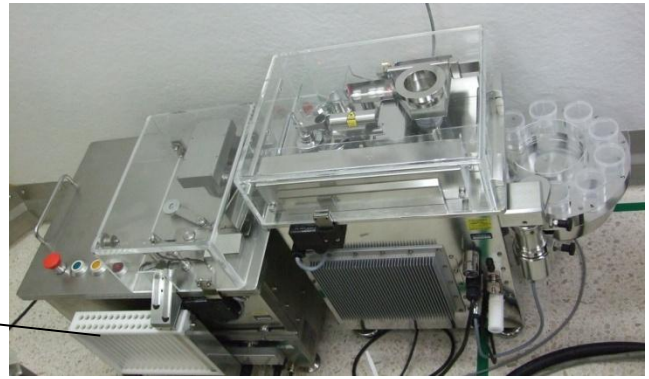
Operational use of the Tandem system

NIR spectrometer

Tablet locator

Tablet nest

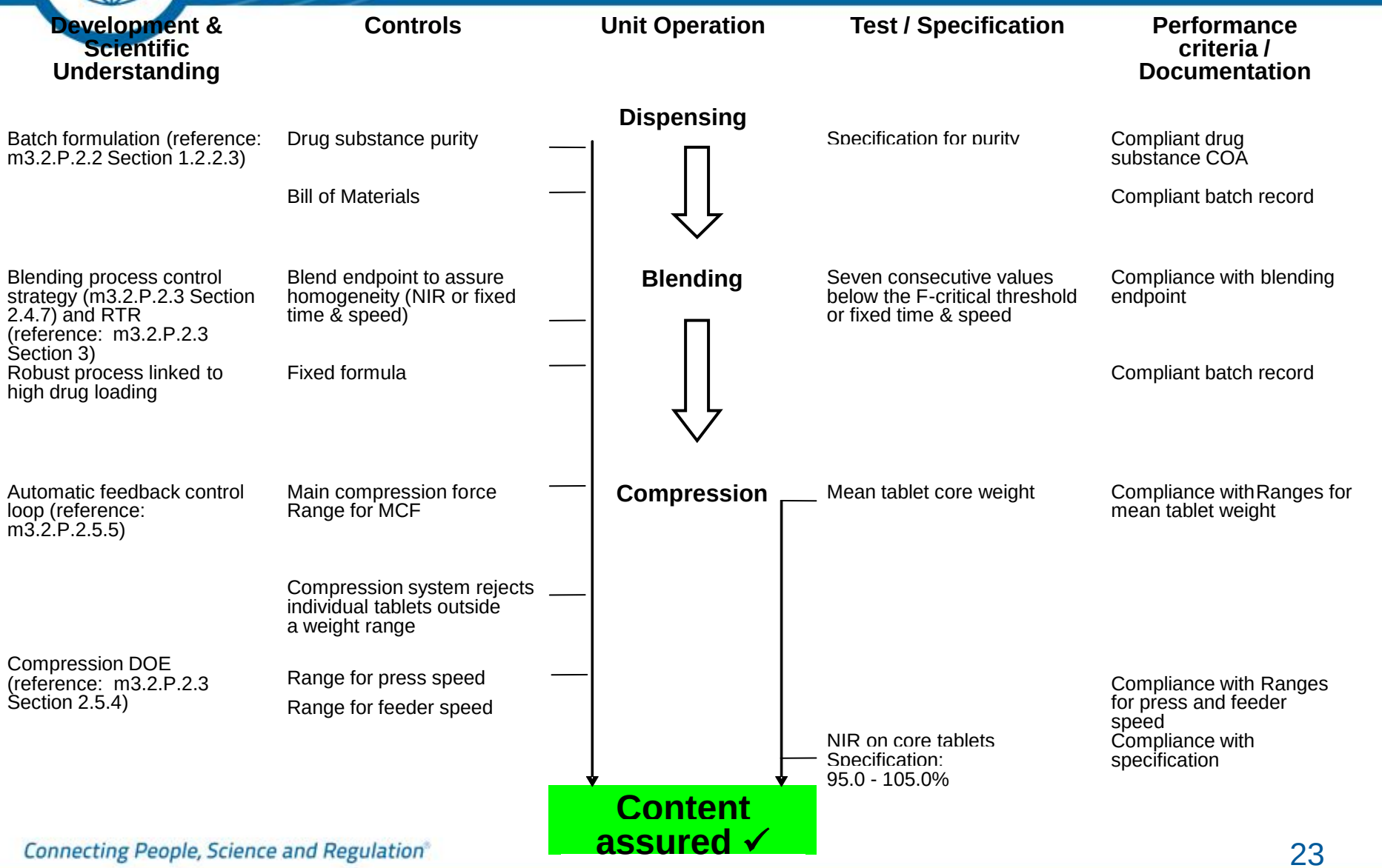




Tablet collector

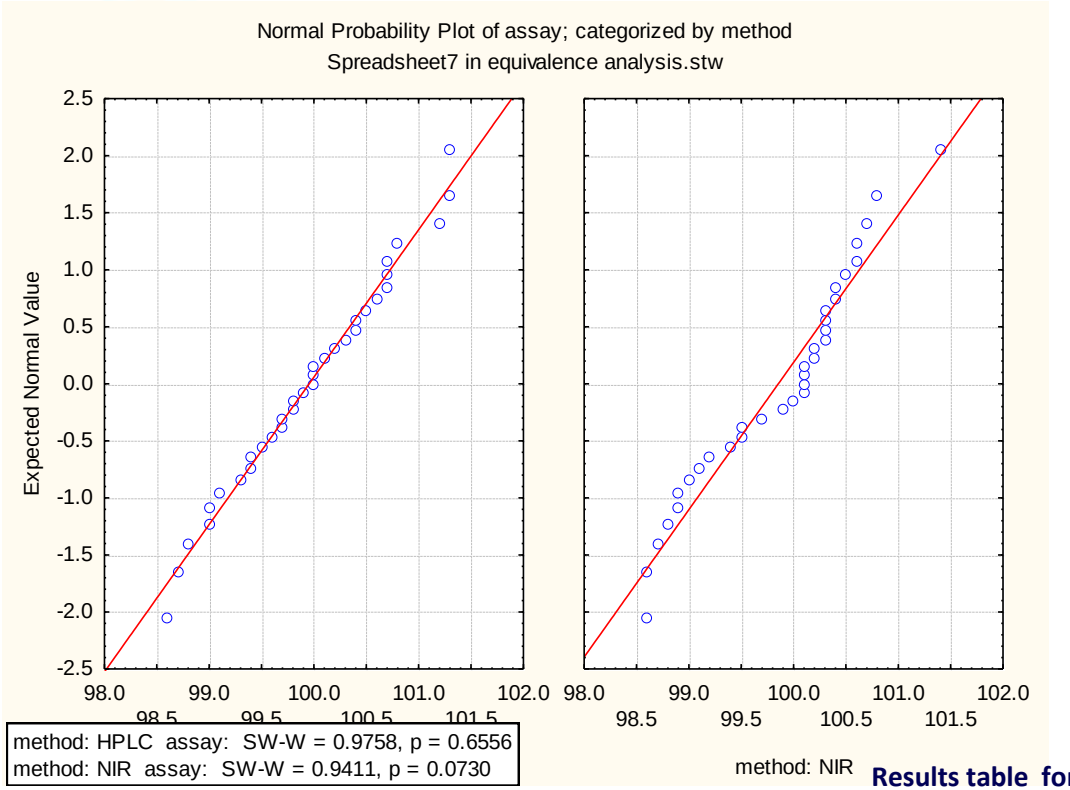
Balance
(IPC for weight and used in NIR calculation)

Tablet hopper


Development & Scientific Understanding
Controls
Unit Operation
Test / Specification
Performance criteria / Documentation
Dispensing
Batch formulation (reference: m3.2.P.2.2 Section 1.2.2.3)
Drug substance purity
Specification for purity
Compliant drug substance COA
Bill of Materials
Compliant batch record
Blending
Blending process control strategy (m3.2.P.2.3 Section 2.4.7) and RTR (reference: m3.2.P.2.3 Section 3)
Blend endpoint to assure homogeneity (NIR or fixed time & speed)
Seven consecutive values below the F-critical threshold or fixed time & speed
Compliance with blending endpoint
Robust process linked to high drug loading
Fixed formula
Compliant batch record
Compression
Automatic feedback control loop (reference: m3.2.P.2.5.5)
Main compression force Range for MCF
Mean tablet core weight
Compliance with Ranges for mean tablet weight
Compression system rejects individual tablets outside a weight range
Compression DOE (reference: m3.2.P.2.3 Section 2.5.4)
Range for press speed
Range for feeder speed
Compliance with Ranges for press and feeder speed
NIR on core tablets Specification: 95.0 - 105.0%
Compliance with specification
Content assured ✓

NIR method for the determination of content equivalence NIR/HPLC

Normal probability plots of the data for HPLC and NIR methods along with SW test statistics.



- The difference between the mean of the 30 batch NIR result and mean of the 30 batch lab based HPLC result is no greater than 2% at the 95% significance level.

- The drug product content of each of the 30 batches as measured by NIR and HPLC meets the required specification for label claim.(95.0 - 105.0% for EU)

Acceptance criteria Met

Results table for equivalence between HPLC and NIR methods.

T-test for assay grouped by method (Spreadsheet7 in equivalence analysis.stw)
Group 1: HPLC
Group 2: NIR
The tests are based on pooled variances

Variab	Mean HPLC	Mean NIR	t-value	df	p	Means Difference	Std.Err.Diff	90% Lower Confidence Limit	90% Upper Confidence Limit
assay	99.955	99.855	0.551	64	0.58345	0.100	0.181	-0.203	0.403

PAT - Model lifecycle 1of 2

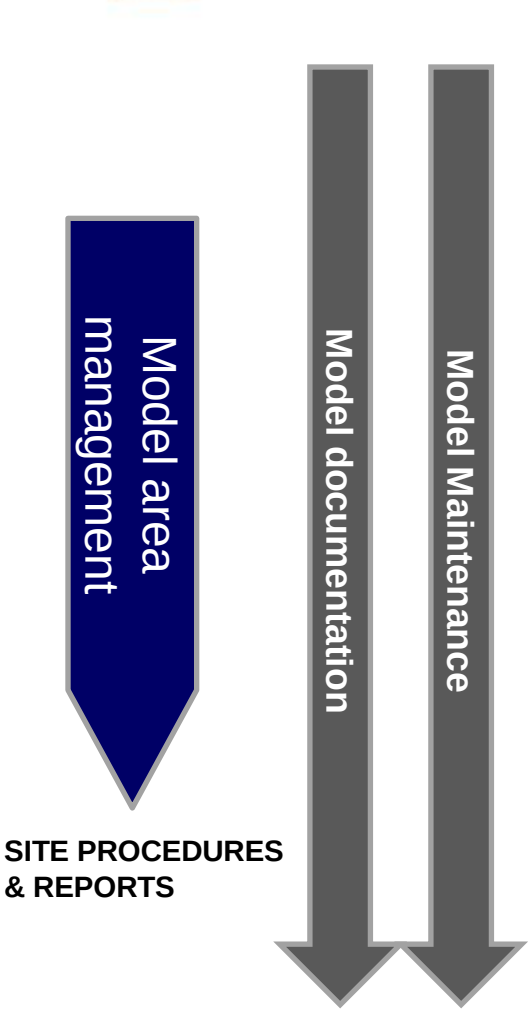
Model development	Model Implementation/transfer	Model in routine use
Select model solution **Develop** **Verify**	**Transfer** **Implement** **Verify**	**Monitor** **Maintain/update** **Up-version** **Verify**
Model development **Site Procedures & Reports**	Model transfer **Site Procedures & Reports**	Model Governance **Site Procedures & Reports**

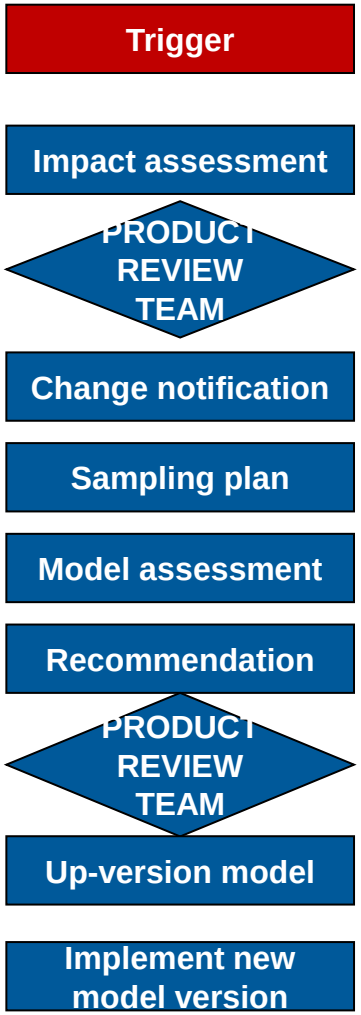
Document Model and Model Changes

Secure Storage of active Model Version

Model Version Control

PAT- Model lifecycle 2of 2





- Material change
- Atypical/OOS or Deviation
- Trending of model performance indicators
- Process/Product trending
- Equipment/Instrument change
- Periodic full end product testing
- Periodic Product Review
- Annual Stability testing
- Annual model review
- Other

✓ What was approved

End point determination

- ✓ **Granulation:** Based on calculated parameter (Work) from process data.
- ✓ **Drying:** Via NIR to consistent moisture value
- ✓ **Blending:** Via NIR utilizing a model to determine non causal variability limits

Real Time Release Testing Proposed for All CQA's

- ✓ **Identification of Tablets:** Via NIR
- ✓ **Description of Tablets**: By inspection after coating
- ✓ **Drug-related impurities:** Controlled during drug substance manufacturing based on mechanistic understanding of impurity formation and clear evidence of stability for Drug AA tablet
- ✓ **Drug Content:** Via NIR; RTRT implementation after parallel testing batches via Follow Up Measure (FUM)
- ✓ **Uniformity of Dosage Units:** by weight variation
- ➢ **Dissolution:** Based on Design Space across 2 Unit Operations, SPC Monitoring for Input Material Attributes and Several other variables. Parallel Testing. Further work with MSPC. (DISCUSSION)

Assessor's Views Follow

Assessors views 1

- An ideal application for use of the QbD concept in establishing Real-time-release and Design space

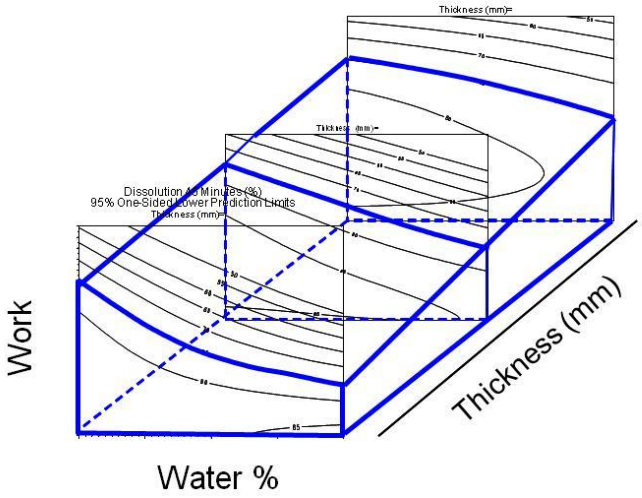
  - Simple immediate release formulation with high content of drug substance
  - Conventional manufacturing process
  - Stable drug substance and drug product
  - Dose proportional strengths
  - Main issue poor solubility of drug substance
  - No major issues identified in Day 120 LoQ
  - In total 31 other concerns, 11 directly related to QbD

Assessors views 2
General Observations

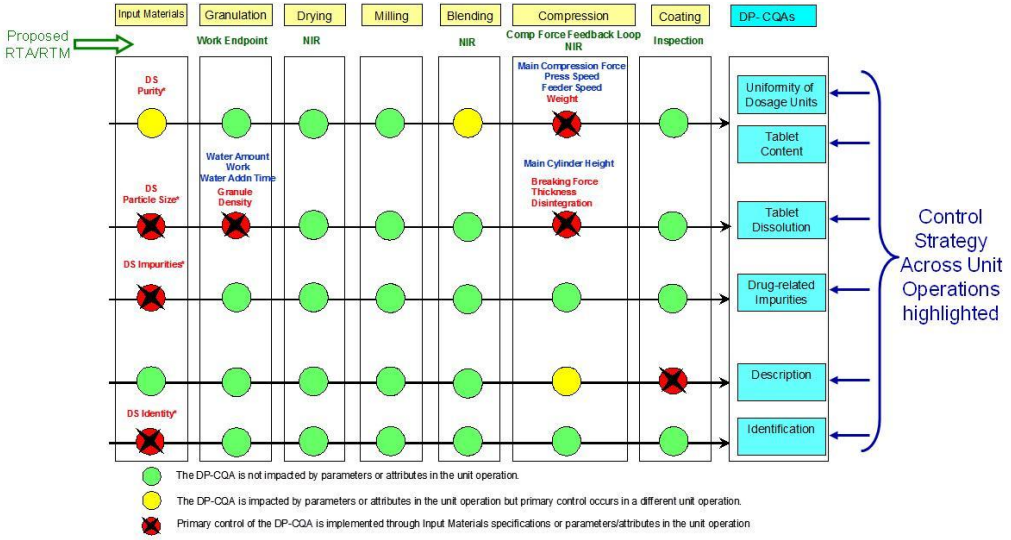
- Dossier
  - Extensive descriptions of QbD in S2, S4, P2, P3 and P5
  - Huge amount of data
    - batches and DoE
  - Illustrative figures and tables throughout the development sections
  - Presentation of the risk assessment and justification for the choice of CQA in the formulation and manufacturing process
    - Drug substance/drug product risk matrix, MVA, fishbone etc.
  - Impressive purging and fate studies for impurities and degradation products
    - Flowcharts
  - Presentations of Design Space for dissolution and control strategy for RTRT
    - Three dimensional figure
    - Illustrative table in colours

Assessor's Views 3: Clear Presentations of Design Space and Control Strategy

Dissolution Design Space



Drug Product Control Strategy



* Control of the Drug Substance CQA is described in m3.2.S.2

Assessors views 4: General observations

- Dossier
  - Development of the dossier was made prior to finalisation of the ICH Q8/Q9/Q10 guidelines and ICH terminology was not always followed, which in some situations made it difficult to follow the information in the dossier in relation to guideline requirements.
  - Although the DoE used for establishing the Design space was done on commercial scale, it was not clearly indicated in the dossier
    - However, applicant clarified it by responding that indeed the data were on commercial scale batches
  - Post approval change management plans were proposed too early without proper justification for changes in e.g.
    - Change in suppliers of starting materials, batch size and equipment used in the manufacturing process for the drug substance in relation to manufacturing process
    - Change in equipment used in the manufacturing process for the finished product in relation to Design Space
  - <u>Other (applies to Drug Substance)</u>
    - Not apparent whether a Design Space was proposed for the drug substance or sets of proven acceptable ranges

Assessors views 5: Specific Observations - Dissolution

- Design space and RTRT
  - Supportive work performed
    - Commercial Scale DoE across 2 unit operations
    - Large amount of data at Commercial Scale
    - Trending of several process parameters (additionally to CPP's and CQA's) (MSPC subsequently followed once enough data were collected)
  - Verification of Design Space and RTRT – control strategy
    - Post-approval parallel testing of 30 batches
    - Additional testing of 200 mg strength (less than 30 batches)
  - Proposed change management plan should be justified. Otherwise variations might be requested in case of changes
    - Equipment, Upscale, New suppliers
  - Observations during pre-approval inspection
    - Dissolution testing according to S2 – Detected by Multivariate Analysis, MSPC
    - Setting specification

Assessors views 6:
Specific Observations – ID, Assay and UoC / PAI

- RTRT
  - Supportive work performed
    - Extensive data sets for calibration
    - Internal & external verification
    - Homogeneity of blending assured by PAT / or length of blending
  - High content of drug substance and low content of degradation products
  - Verification of RTRT – control strategy
    - Post-approval parallel testing of 30 batches

❑ PAI Comments (Joint PAI FDA & EMA)

- GSK were excellent in their provision of information and discussions
- The product specific inspection was of great value to quality assessors.

Assessors views 7: Comments & Challenges

- Using QbD approaches in an application gives valuable information to both MAH and authorities. The efforts should be measured against the value of obtaining a Design space and/or RTRT.

- Assessment is much more dependent on on-site knowledge in order to make a proper evaluation of the use of PAT tools in relation to the control of process parameters during manufacture. A knowledge which can only be obtained as part of a pre-approval inspection

- Evaluation of statistical calculations (multivariate analysis) and choice of DoE models on which QbD approaches are based upon are challenging and require advanced statistical knowledge. A knowledge which common quality assessors and GMP inspectors usually do not have
  - How much (raw) data should be included in the dossier?

Industry and Assessors. Joint Comments

Best Practice Recommendations

- Utilize ICH terminology
- Dossier
  - Clearly state whether or not a Design Space is proposed in the dossier (3.2.S and 3.2.P)
    - Relation to PAR

- Presentation of QbD should be adequately detailed explaining the rationale for choices of CQA, DoE, Ranges etc. The purpose is to provide the assessor with a sufficient amount of data without overloading him/her with information.
- If a Design Space is proposed it should be clearly presented (for example, if the design space is a multivariate model give equation, or other visual representation)

- Defining CQAs and CPPs are crucial for implementing QbD and should be carefully described in an easy and understandable way
  - Description of risk assessment very important for understanding
  - For Design Space flexibility and RTRT maintenance it would be a good practice to include considerations for (eg.ways of addressing) changes in quality of drug substance (e.g. use of new suppliers of starting materials), quality of excipients (e.g. suppliers and particle sizes), influence during stability etc.

Best Practice Recommendations

- Carefully explain and justify the assumptions and statistics used for MVA and DoE as necessary (see ICH Points to consider for Modelling)
- Using QbD approaches in an application gives valuable information to both MAH and authorities. Applying on a simple product may provide foundations of knowledge for future products.

- Multivariate Statistical Process Control including several variables (material attributes & other process parameters) additionally to Design Space helps to support RTRT for predicted quality (eg dissolution)

- Parallel Testing Considerations
  - Dissolution: soft sensor (predicted quality)
  - NIR for content: Analyser based, high API content: when is parallel testing necessary ?

Best Practice Recommendations

•Follow ICH points to consider for modelling (High, Medium, Low risk models).

- Clearly state calibration samples and validation samples for Spectral Calibrations

- Model Maintenance plans

• Collaboration / Interactions with Regulatory Authorities for Innovative PAT or Modelling Methods

•The need for a pre-approval site inspection / visit could depend upon what is proposed in terms of in-process controls during manufacture and the PAT tools used

Questions for Day 2

Development of Design Space, Use of MVA models, Calibration Models

- How many raw data used for the MVA (if any) should be included in the dossier?
- How many batches should be tested in parallel prior to approval of RTRT?

Post Approval Changes

- Changes of Spectrophotometers; Addition of new lines