Application of PAT for Tablet Analysis

Case examples from Novartis

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Agenda

- PAT@Novartis
  - Organization
  - Business Drivers and Cases

- NIR Spectroscopy for Tablet Analysis
  - Motivation and Advantages in terms of cost and quality
  - Case example 1: Off-line implementation
  - Case example 2: At-line application

- Conclusion and Outlook
Definition QbD (Quality by Design)

New approach to develop and control processes and the quality of the products

- Development Domain
- Risk Assessment
- Design Space
- Real Time Release
- Process Understanding
- Production Domain
- Process Control
- QBD
- PAT
- DoE
- MVDA
- PAT for Tablet Analysis

3 | ISPE | Liesum | 19th of April | PAT for Tablet Analysis | Business Use Only
Two PAT perspectives

- QbD
- Real Time Release
- Process Validation
- Continuous Process Verification

Decrease variability and 
# of deviations
Increase level of QA

PAT

Quality

Increase of efficiency and yield

Process

- Feedback Control
- Endpoint determination
- Energy savings
- Yield improvements
PAT applications – Pharmaceutical Operations

- Granulation
  - Scale up and monitoring

- Drying
  - Endpoint determination

- Blending
  - Endpoint determination

- Compression/Film Coating
  - Monitoring and Real time release

100 % ID testing for excipient and API by NIR and Raman
Content Uniformity by NIR

Xbar Chart of 100 Tablets

Summary for 100 Tablets

Concentration Correlation Plot
Advantages of NIR for Tablet Analysis

Overview

- Very fast, since no dilution/sample preparation is necessary
- Enabler of analysis of large sample size as recommended by EMA for continuous process verification
- Non-destructive
- Minimum chemical disposal and exposure
- Very robust and reproducible and therefore transferable between sites
- Sensitive to physical properties of the tablets
Limitation and constraints

Overview

- Sensitivity limited to approx. 1%, no trace method and not adequate for analyzing impurities
- Transmission not feasible for very thick tablets and for special coatings
- Need for chemometric evaluation and expertise
- Only applicable for polar organic molecules with C-H, O-H and N-H bonds
- Sensitive to process variability
Quality benefit: Increase of Sample Size

- The increase of the sample size from 10 to 100 – 1000 leads to
  - Better understanding of the distribution type of the tablets' content
    - Normal type distribution
    - Unimodal vs. bimodal distribution
    - Presence of outliers
  - Lowering the confidence interval for the coefficient of variation (relative standard deviation)
  - Dynamic information of the compression run
  - Increases the chance detecting strong outliers
Business benefit
Reducing QC labor cost

Very simplified business case:

- **Investments:**
  - Spectrometer 100,000 Euros
  - Qualification effort 100,000 Euros
  - Development and validation effort 300,000 Euros

- **Benefits**
  - 1 CU + ID determination need 8 h lab work: 500 Euros
  - For a product with 1000 batches a year: 500,000 Euros

- Based on batch volumes the return of investment is approx. 1-3 years.
Case Example 1

**Offline Application**

- To develop a robust UDU-CU method by NIR spectroscopy for rapid analysis
  - Equivalency to the reference HPLC method
  - Transferability of the method across instruments and to production site(s)
Mount PAT
*The GMP “North Route”*

**The Matterhorn, CH**

- Continual Improvement
- Maintenance
- Submission and Inspection
- Validation
- Development and Calibration tablets
- Instrument Qualification
- Feasibility and instrument selection
Regulatory references

Guidelines from USP, FDA and Pharm. Eur.

- USP <905> Uniformity of dosage units
- USP <1119> NIR spectroscopy
- ICH Q2(R1) Validation of analytical procedures
- Ph.Eur. 2.9.40 Uniformity of dosage units
- Ph.Eur. 2.9.49 Handling of large sample sizes
- Ph.Eur. 2.2.40. NIR spectrophotometry
- Guideline on the use of NIR by the pharmaceutical industry and the data requirement for new submissions and variations, EMEA 2003/2009
Development
Development
General statement

- A detailed vendor evaluation and feasibility investigation concerning the modalities was carried out prior to the final development of the methods.

- For each dosage strength a dedicated method was developed in diffuse transmission on an off-line instrument.

- The development and validation was carried out in the pharmaceutical development unit in East Hanover (NJ) in the US and then transferred to the production site in Switzerland.
What to consider first....

- **Calibration tablets**
  - Range?
  - Composition/calibration design in order to avoid chance correlations
  - Representative?

- **Acquisition settings**
  - Resolution and number of scans determine overall acquisition time

- **Challenges**
  - Placebo tablets
Methodology

Calibration tablets

NIR

Reference method (HPLC)

NIR calibration spectra

API content

Chemometrics

NIR validation spectra

Calibration Model

API content of validation tablets
Validation
## Method Validation

**ICH Q2**

### Table

<table>
<thead>
<tr>
<th>Type of analytical procedure characteristics</th>
<th>IDENTIFICATION</th>
<th>TESTING FOR IMPURITIES quantitat. limit</th>
<th>ASSAY - dissolution (measurement only) - content/potency</th>
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<tr>
<td>Accuracy</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Precision</td>
<td></td>
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<tr>
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<tr>
<td>Quantitation Limit</td>
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<td>Linearity</td>
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<td>+</td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Data structure for Validation

Model development

- Validation Protocol is issued.
- Model is fixed.

Calibration set (used for Modeling)
- Linearity
- Accuracy
- Specificity
- Precision: Repeatability
- Precision: Intermediate precision
- Robustness (Hardness, Thickness)

Test set (Internal Validation)

Validation Set (External Validation)
- Accuracy at target
- Precision: Repeatability

Validation Report
- Model implementation
Method Transfer
The same tablets were analyzed in center A (USA) and then shipped to Switzerland for a second analysis.
Case Example 2
Objective

- To develop a robust UDU-CU method by NIR spectroscopy for at-line analysis together with physical properties (weight of the tablet)
  - Equivalency to the reference HPLC method
  - Fully automated and robust at-line system with accurate result, low maintenance effort and feedback control option
Case Example 2

- Taking the next step: At line measurement
  - No involvement of an operator
  - Timely measurement as the compression is ongoing
  - Large sample sizes
  - Real Time Release Testing
  - Combine physical with chemical data (weight and thickness/content)
  - Possibility of feedback or stop process
New Challenges apart from Spectroscopy

- **Mechanical Robustness**
  - Smooth transfer of tablets from the compression line to the analyzer
  - Correct positioning of tablets in the sample holder

- **Automation**
  - Interface between NIR equipment and compression machine to
    - To “order” new tablets
    - To stop the process if significant deviations are observed
  - Reporting of results including new statistics
  - Alert management
  - User friendly
Balance for getting the best solution

Automation

Control/Alert Management
User friendliness
Data handling

Accuracy

Spectroscopy

Mechanics

Robustness
CU by NIR

Tablet analysis

- **Goals and objective**
  - Process monitoring assuring process stability (essential for continuous manufacturing)
  - Assessment of capability and distribution
  - Real time release for CU and Identity
Change for confidence intervals for mean and standard deviations

- CI for standard deviation is for n=10 is very broad though the standard deviation is main information describing CU
Process Validation and CPV

- Within a process validation an intensive sampling is performed in order to better characterize the process dynamics and variability, e.g. 10 tablets at start, middle and end or applying the Bergum approach with defined sampling intervals.

- After process validation the CU is only reduced to the analysis of 10 tablets

- With CU NIR you can apply the validation requirements on every batch in the sense of continuous process verification
CPV of a compression run using NIR data

- Intra batch variability: potency as a function of time

- Inter batch variability: CU as function of batch number
Conclusions

- Important aspects to be considered
  - Convince people in QA and production for a change in mindset
  - A lot of training is needed to ensure that necessary skill set and understanding is established
  - A PAT project is not completed right after validation, then it actually starts with automation, maintenance and using it at a daily basis
  - and ....

PATience