NIRS, PAT, RTR testing
EU experience and regulatory perspective

Heidelberg, Germany

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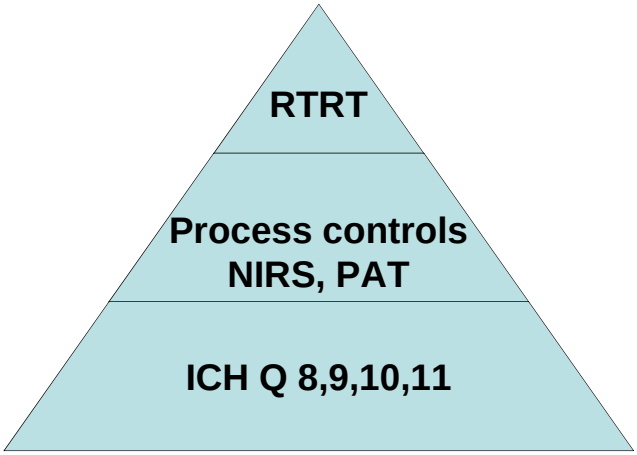
Overview of the presentation

- General considerations
- Cases submitted in Europe
- Models / level of data required in the dossier
- EU guidance on RTR testing
- Collaboration between assessors and inspectors
- Conclusion

General considerations

- ICH Q 8,9,10,11 platform for establishing RTR testing mechanisms
- RTR testing based on information collected during the manufacturing process on critical parameters or attributes
- PAT, NIRS and RTR testing are under the umbrella of QbD



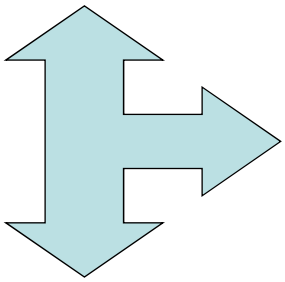
General considerations

Linkage between NIRS, PAT and RTR testing

Control of process parameters / DS parameters (example: granulation parameters, drying parameters).

and/or

Monitoring of product attributes (particle size, content uniformity, hardness, water content).



<u>This might include NIRS, PAT and/or prediction models</u>

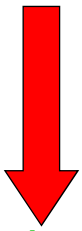
Applied to one or multiple unit operations (granulation, blending, tabletting).

Replaces end product testing in routine for batch release

General considerations on MSPC

- Definition (ICH Q8R): ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls.

Model derived from MSPC data



Predict end product specifications

Replaces end product testing by material and process controls

General considerations on RTR testing

Simple

- pH in bulk solution
- Water content on line or at line
- Tests for Oral solid dosage forms (disintegration)

More complex

- Assay by NIRS at line
- Content uniformity by NIRS at line
- Impurity profile based on design space
- Dissolution based on design space

Active substances, intermediates and finished products
Chemical and biological products
Not applicable to investigational medicinal products
New products and well established marketed products (legacy products)
Addresses data requirements for applications that propose RTR testing for release

Case 1: NIR for Blend uniformity, PAT application

- Determination of an end-point for blend uniformity using NIR is proposed instead of fixing a blending duration.
- Blend uniformity end-point is attained after the following criteria are met and maintained for 5 consecutive minutes:

  - NIR predictions are within 90.0 – 110.0%

  - Moving block standard deviation of NIR predicted blend (%) (block size, n = 10) must be < 2.5%
- A feedback loop in SCADA (Supervisory Control and Data Acquisition) has been installed to stop the blending process once the acceptance criteria are met.

Replacement of the number of mixer rotations by a NIR blending end point cannot be accepted without a description of the NIR method and a validation of its suitability to monitor blend uniformity.

Justification of the acceptance criteria for the blend uniformity by NIR was provided. The criteria were established using NIR blend uniformity monitoring data acquired from 3 target commercial batches and 12 full scale confirmatory DoE batches.

Case 2: NIR at line, alternative method for batch release

- A Near Infra Red (NIR) method has been developed for finished product testing at release (identity, assay, uniformity of dosage units). Clarifications have been raised on the method description, calibration methodology and model validation.

Definition of the scope of the method
Independency of the samples used in the calibration set
Variability studied over the range of DS
Range covered by external validation
Rejection of samples outside the scope
Information on parallel testing
Use of reference method
Second criteria to disclose large deviating units

External validation: 85-115% range covered
Second criteria implemented as part of the specifications.
Parallel testing: 6 commercial batches.

Case 2: Drug product specifications (abstract) Film coated tablets – low dosage form

Test	Test method	Acceptance criteria
Identification [1,2]	NIR	Positive identification
Identification	LC	The retention time of the main peak in the test chromatogram is comparable to that of the reference standard
Assay [1,2]	NIR	95.0 – 105.0% of label claim (mean value of all samples from Uniformity of Dosage Units testing
Uniformity of Dosage Units [1,2]	NIR	Large sample size

Number of tablet cores sampled	100 to 133	134 to 166	167 to 175	176 to 199	200 to 233	234 to 266
Acceptable number of tablet cores outside 85.0 – 115.0% LC	3	4	5	5	6	7
Acceptable number of tablet cores outside 75.0 – 125.0% LC	0	0	0	1	1	1

[1] Samples from stratified core sampling will be used to satisfy the test.

[2] The NIR method will be used for routine product release.

Case 3: Impurity level based on DS parameters , RTRT

- Design space developed on crystallisation
- CQA: 4 HBA and residual THF
- Extensive list of questions regarding development of Design Space

Details of the FMEA
Ranges explored in the DoEs
Batch size included in the DoEs
Tabulated data for DoEs supporting DS
Details on the statistical results
Scale up effects supported by experimental data

The specific identified impurity content will not be performed routinely at the time of release: controlled via crystallisation design space process parameters.

Case 3: Drug substance specifications (abstract)

Test	Test method	Acceptance criteria
Residual solvents [a]	**GC** [d]	Cyclohexane NMT 0.1% Ethanol NMT 0.1% Pyridine NMT 100 ppm THF NMT 720 ppm Toluene NMT 890 ppm Xylene NMT 0.1%
	NIR on-line	Ethanol NMT 0.1%
	Real time release	Cyclohexane NMT 0.1% Pyridine NMT 100 ppm THF NMT 720 ppm Toluene NMT 890 ppm Xylene NMT 0.1%
Water	**NIR on-line**	NMT 0.5%
Specific identified impurity [b]	**HPLC** [d]	4-Hydrazinobenzoic acid NMT 0.5 ppm
	Real time release	4-Hydrazinobenzoic acid NMT 0.5 ppm
Assay [c]	**HPLC** [d]	98.0 – 102.0%
	Real time release	98.0 – 102.0%

[a] The residual solvents will not be performed routinely at the time of release (except for ethanol routinely controlled by NIR) as they are controlled via design space on drying parameters.
[b] The specific identified impurity content will not be performed routinely at the time of release as it is controlled via design space on crystallisation parameters.
[c] The assay will not be performed routinely at the time of release as it is controlled via design space on crystallisation and drying parameters.
[d] These alternate methods may be used for batch release in certain conditions (e.g. equipment failure or legal restrictions such as pharmacopoeias).

Case 4: Dissolution based on DS parameters, RTRT

- Design space developed on granulation step
- CQA: Granule surface area
- Extensive list of questions regarding development of DS

Criticality: risk assessment methodology, scores
DoEs: type of design, resolution, interactions, ranges explored
Batch size included in the DoEs
Tabulated data for DoEs supporting DS
Validation of reference method
Scale up and verification of DS at commercial scale

The dissolution test will not be performed routinely at the time of release:
controlled via the granulation design space process parameters,
and the GSA and disintegration in-process tests.
Dissolution testing will be performed on stability.

Case 4: Drug product specifications (abstract) Film coated tablets

Test	Test method	Acceptance criteria
Dissolution [a]	Ph.Eur. 2.9.3, UV	Shall comply with the requirements of the Ph. Eur. Q = 75% at 45 minutes, if tested
Uniformity of Dosage Units [b]	Ph. Eur. 2.9.40 by mass variation	Shall comply with the requirements of the Ph. Eur., if tested

[a] The dissolution test will not be performed routinely at the time of release as it is controlled via design space, granule surface area and disintegration in-process tests (RTRT based on relationship established between dissolution and in-process tests).

[b] The uniformity of dosage units test will not be performed routinely, however all batches would pass the acceptance criteria if tested (RTRT based on process parameters and control of tablet weight in-process).

Case 5 : MSPC for granulation unit operation, monitoring

Variables/ Process parameters used in the model:

Flow liquid feed
Mixer power rate of change
Mixer power (electrical)
Total Liquid Added
Mixer power (calculated)
Mixer torque
Liquid feed pump speed
Bowl pressure
Mixer speed
Chopper speed
Product temperature
Bowl temperature

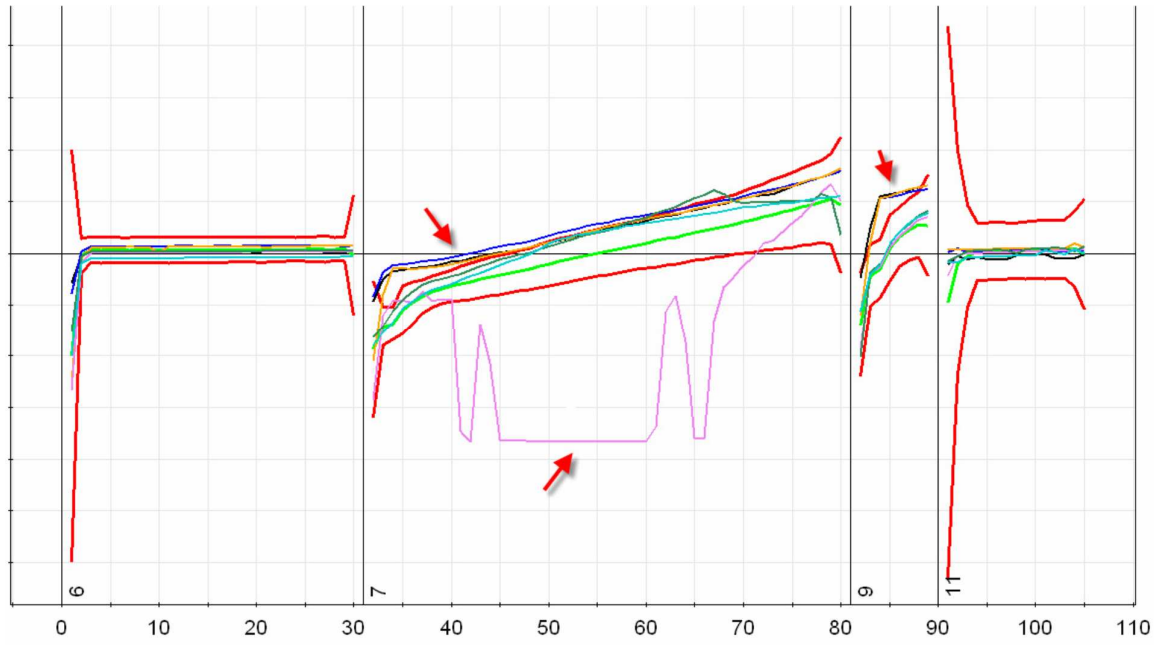
Number of granulation batches for calibration and internal validation: 114
Number of granulation batches for external validation: 6
Scale: commercial scale
Model: PLS

Case 5 : MSPC for granulation unit operation, monitoring

For the first PLS, components *Mixer Power*, *Liquid Added* and *Product Temperature* have the largest influence and are significantly correlated to each other, which is in good agreement with the expectation. By adding more water the power consumption is increasing and by introducing energy into the system also the product temperature is rising.

For the second PLS, components *Chopper Speed* and *Mixer Speed* are the most important factors which impact is independent from the process variables influencing the first factor. *Float Liquid feed* and *Liquid Pump Speed* have an influence on both principal components.

Case 5 : Control chart: detect deviating batches, monitoring



Case 5 : MSPC for drying unit operation, monitoring

Variables/ Process parameters used in the model:

Spray rate
Inlet air volume
Inlet air humidity (absolute)
Inlet air humidity (relative)
Spray air pressure
Pressure before product sieve
Pressure after product filter
Spray quantity (*0,1_kg)
Inlet air temp after cooling

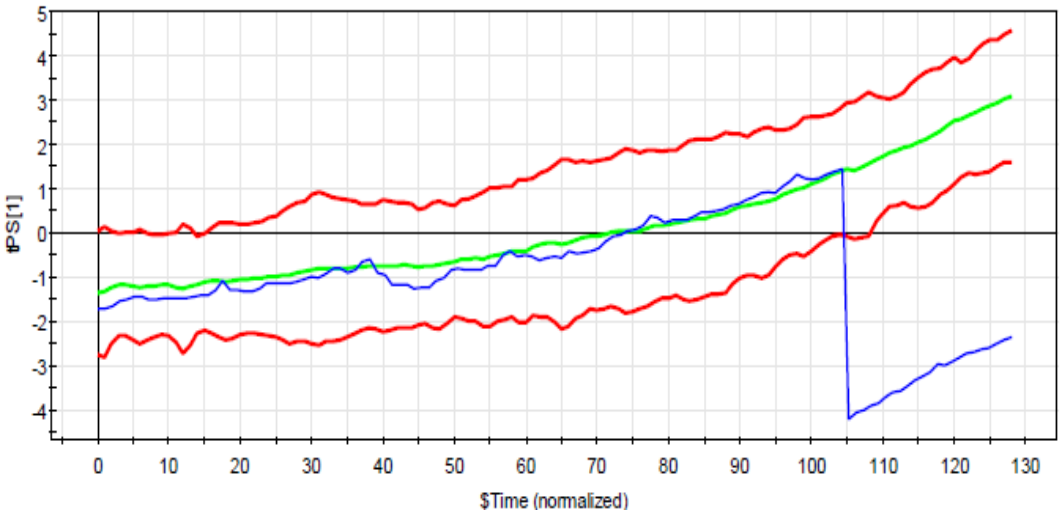
Number of drying batches for calibration and internal validation: 121
Number of granulation batches for external validation: 6
Scale: commercial scale
Model: PLS

Case 6 : MSPC for drying unit operation, monitoring

For the first PLS, components *Product Temperature* and *Outlet Air Temperature* have the largest influence and are significantly correlated to each other, which is in good agreement with the expectation. If the material is dried the introduced energy is no longer absorbed for the evaporation of water. Consequently the temperature of the dried powder is increasing as well as the outlet air.

For the second PLS, components *Inlet Air Humidity absolute and relative,* and *Inlet Air Temperature after Cooling* are the most important factors and correlated to each other. These parameters are uncorrelated to *Product Temperature* and *Outlet Air Temperature* as they are more depending on environmental influences. All other parameters seem to have a minor influence.

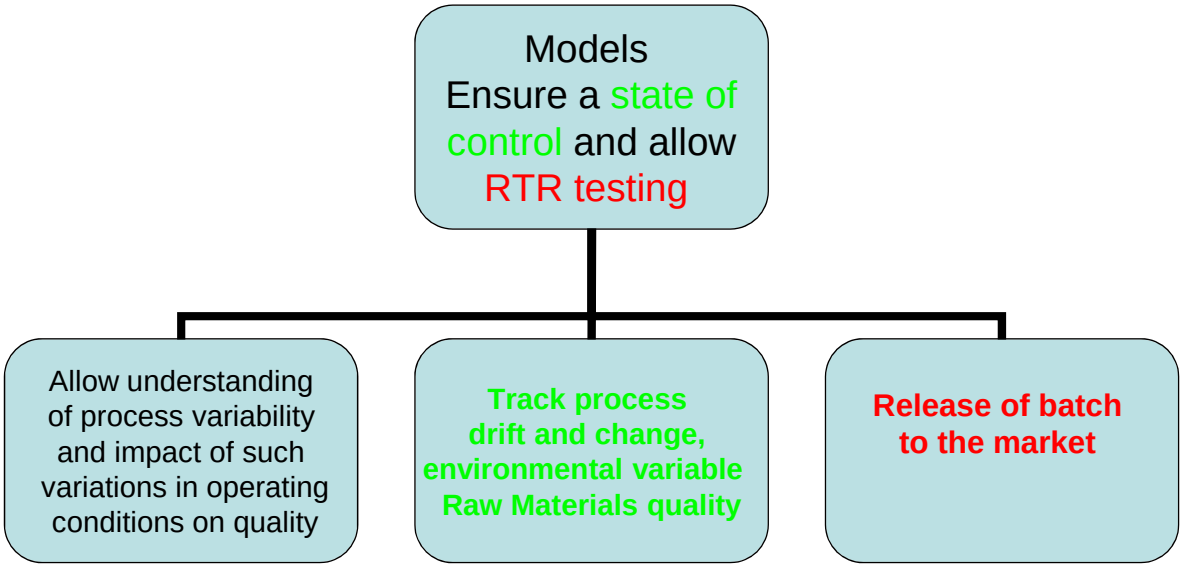
Case 6 : Response of MVDA model to incoming air, monitoring



Models : What is all about?

- Models : a black box ?
- Process control based on MVDA and corresponding models, typically PLS and PCA : Multistatistical process control, NIRS
- MVDA: identify which process variables are influential on the variability and dynamics of the process and analyse how the variables are correlated.

Models : What is all about?



Models : Level of data required in the dossier

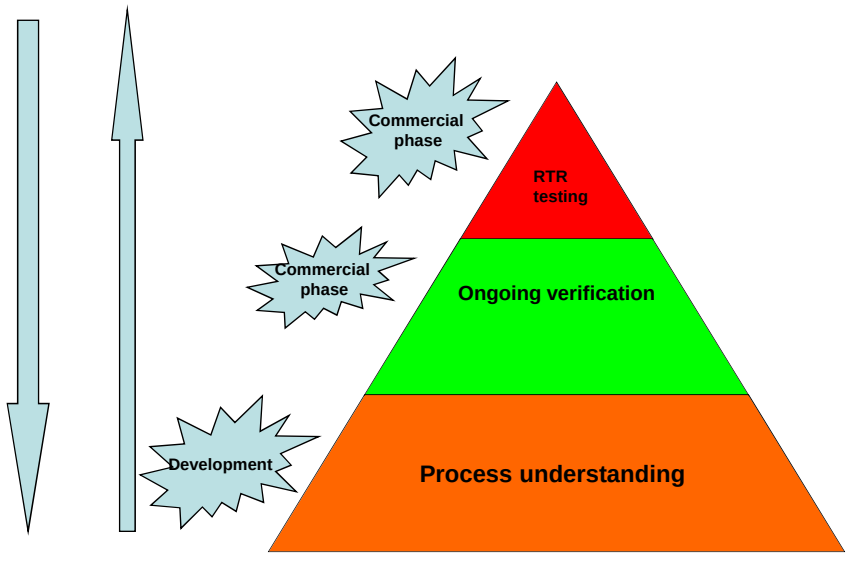
- Depends on the scope of model
- Refers to IWG Points to Consider on classification of models in low, medium and high impact models
- High impact models are models intended for product release

- All potential sources of variability captured in the model
- Data collection: sensors, probes, interfaces
- Batches/samples population
- Composition of sample sets: calibration set/ internal validation/ external validation
- Model lifecycle

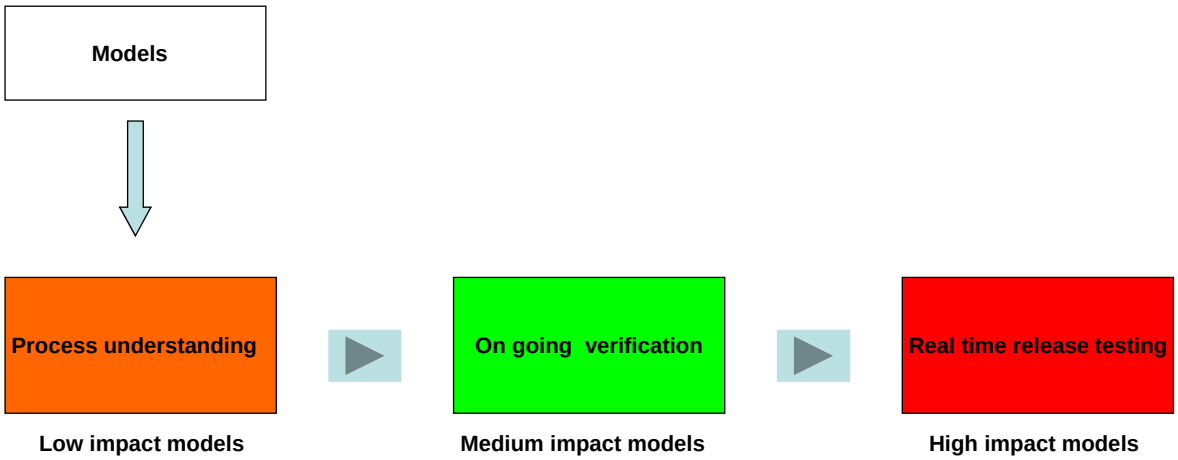
Models : Level of data required in the dossier

- *Low-Impact Models:* These models are typically used to support product and/or process development (e.g. formulation optimisation).
- *Medium-Impact Models:* Such models can be useful in assuring quality of the product but are not the sole indicators of product quality (e.g. most design space models, many in-process controls).
- *High-Impact Models:* A model can be considered high impact if prediction from the model is a significant indicator of quality of the product (e.g. a chemometric model for product assay, a surrogate model for dissolutions).

Models : level of data required in the dossier



Models : Level of data required in the dossier



Guideline on Real Time Release Testing

- **Guideline on real time release testing (RTRT) formerly Guideline on parametric release**
- **Concept so far applied to sterility testing (associated to parametric release): Revision does not introduce new requirements for parametric release (terminally sterilised products)**

- ✓ Introduction of RTR testing requires pre-authorisation by Competent Authority
- ✓ Approval as well as withdrawal are at the discretion of authorities: assessors and inspectors
- ✓ Can be introduced anytime during product lefecycle: new marketing authorisation or variation
- ✓ RTR testing is granted for a specific product on a specific site
- ✓ Product release based on information collected during the manufacturing process
- ✓ It can be total (address each quality attribute) or combined with more conventional end product testing

RTR testing: Testing on Importation

- TOI is a requirement of Directive 2001/83/EC
- Normally means that a complete analysis of the product is requested in an EU member state according to the approved specifications
- RTR testing approved: relief from this testing but identification upon receipt of material will apply (similar to parametric release)

Approval requirements for RTR testing

Data submitted for assessment + **Inspection** + **Parallel testing** Commercial scale

DEPENDS ON THE COMPLEXITY OF THE TECHNOLOY INVOLVED IN THE RTR TESTING

Collaboration between assessors and inspectors

Question and Answer on EMA website

In practical, how does it work?

- **Are GMP inspectors involved in approval of any RTRT submission ?**
- **When should collaboration between inspector and assessors in relation to RTRT start ?**
- **Are data generated during parallel testing (running in period) reviewed by inspectors or by assessors?**

Collaboration between assessors and inspectors

Are GMP inspectors involved in approval of any RTRT submission ?

- Applicant's approach
- Existing experience of the manufacturer with this approach
- Complexity of technology (such as NIR, Raman)

When should collaboration between inspectors and assessors in relation to RTRT start ?

- Proposal for introduction of RTRT in a new MA or variation application
- Assessor should contact the relevant supervisory authority
- Timing of GMP inspection will depend on the availability of relevant data generated at commercial scale

Collaboration between assessors and inspectors

Are data generated during parallel testing assessed by assessors or inspectors ?

- Data submitted to assessors when models (design space or calibration models for complex technology such as NIR *etc*.) are part of RTRT scheme
- Data not available at time of submission: Use post approval change management protocol to submit data
- MA granted on the grounds of finished product testing

Conclusion

All roads lead to Rome

No preferred approach but strong expectations

- Clearly define the scope
- Justify all assumptions and claims regarding criticality, scale, design space, control strategy
- Provide supportive and comprehensive data in tabulated format

For any clarification, seek advice from EU PAT team

Regulatory perspective

- Guideline on Real Time Release Testing (formerly Guideline on Parametric Release): EMA/CHMP/QWP/811210/2009-Rev1 (1st october 2012)
- Question and Answer on collaboration between assessors and inspectors for approval of RTR testing
- Introduction of a new general chapter 2.9.47 (Demonstration of uniformity of dosage units using large sample sizes) in the Ph. Eur.
- Guideline on Process Validation: EMA/CHMP/CVMP/QWP/70278/2012-Rev1 (draft, end of public consultation)
- Guideline on the use of NIRS by the pharmaceutical industry and the data requirements for new submissions and variations: EMA/CHMP/CVMP/QWP/17760/2009-Rev2 (draft, end of second public consultation
- IWG Points to Consider

Thank you for your attention

Questions ?