Analytical Methods and Sampling in the New Manufacturing Paradigm
– a Regulatory Perspective

Dr. Øyvind Holte
Norwegian Medicines Agency
EMA PAT team/ EDQM PAT working party
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Statens legemiddelverk
Norwegian Medicines Agency

Overview

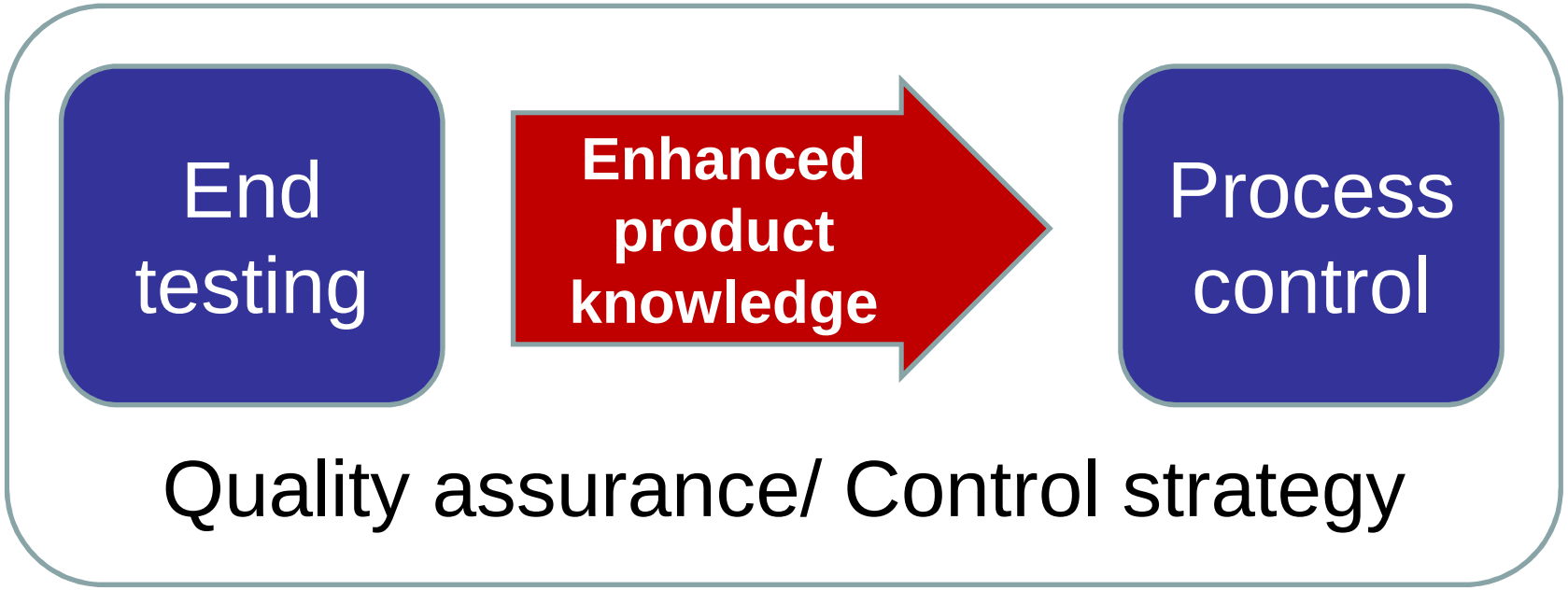
- Demonstrating end-product quality by on-line (PAT) measurements
- Real time release testing: general considerations
- Ph.Eur. 2.9.47: Uniformity of dosage units using large sample sizes
- PAT analytics and calibration models: Pitfalls and opportunities

Regulatory perspective:

- Regulatory guidance
- Dossier requirements for marketing authorizations
- Regulatory experience, advice to applicants

Demonstrating end-product quality by PAT/ QbD

- QbD: Focus shifted from end testing of the product via product knowledge to process control



Demonstrating quality – what is ‘Quality’?

Typically defined by the specification

- Tests
- Acceptance criteria

ICH Q8:

- QTPP: Quality Target Product Profile
- CQA: Critical Quality Attributes

The New Quality Paradigm:
Risk assessment and enhanced approach to development:
Linking material attributes and process parameters to CQAs

‘PAT analytics’ vs traditional analytical methods

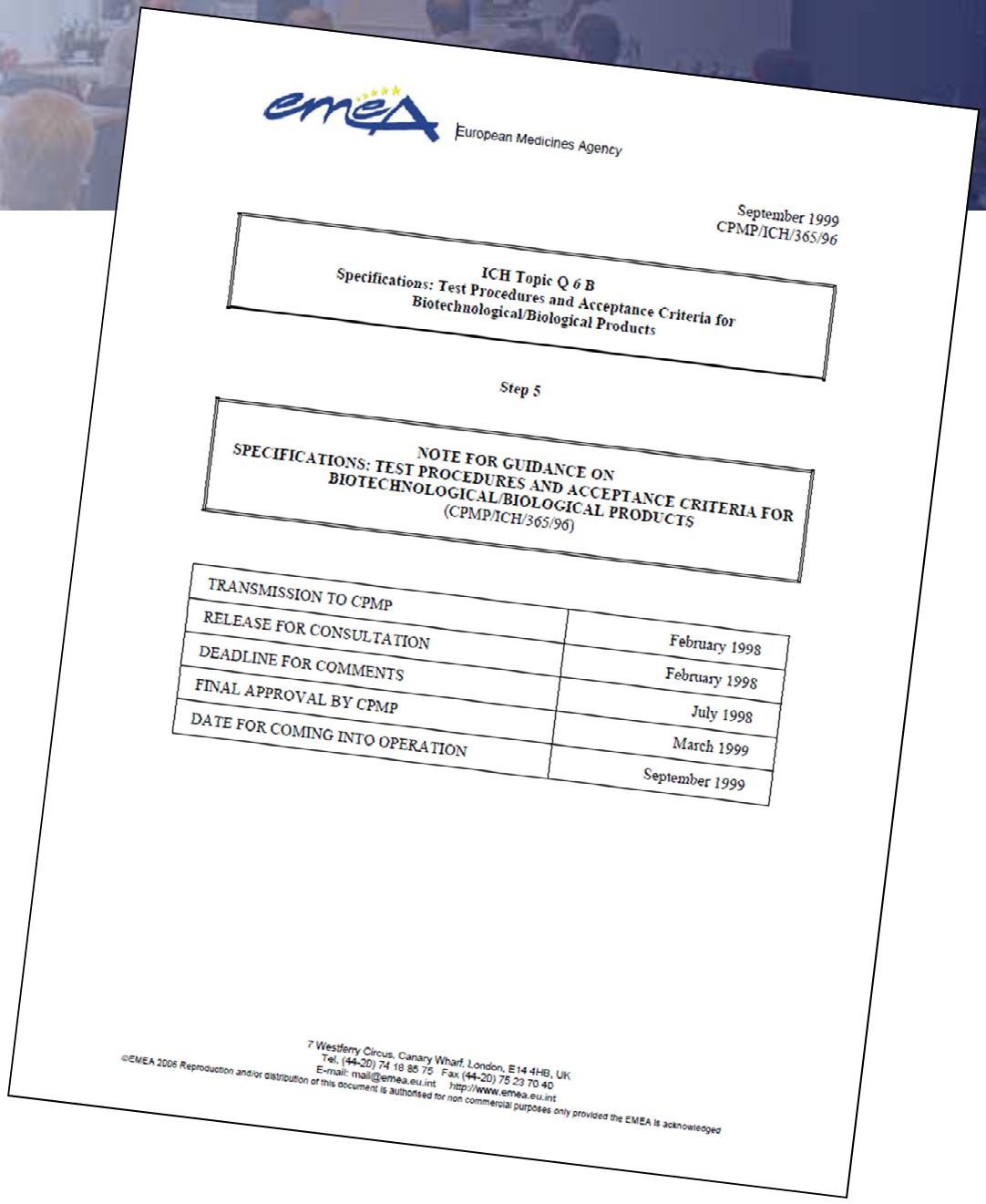
PAT analytics	Traditional methods
▪ On-line/ in-line testing • Starting materials • Intermediates • End products	▪ Off-line testing • Starting materials • Isolated intermediates • End products
▪ Sample size ~100 ++	▪ Small sample size
▪ Non-destructive	▪ Destructive
▪ Immediate results	▪ Delayed results

ICH Q6A, ICH Q6B

General principles for setting specifications

EMA GLs on specific product types

- Inhalation, nasal
- Radiopharmaceuticals
- Medicinal gases
- …



European Medicines Agency

September 1999
CPMP/ICH/365/96

ICH Topic Q 6 B
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Step 5

NOTE FOR GUIDANCE ON
SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS
(CPMP/ICH/365/96)

TRANSMISSION TO CPMP	February 1998
RELEASE FOR CONSULTATION	February 1998
DEADLINE FOR COMMENTS	July 1998
FINAL APPROVAL BY CPMP	March 1999
DATE FOR COMING INTO OPERATION	September 1999

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 85 75 Fax (44-20) 75 23 70 40
E-mail: mail@emea.eu.int http://www.emea.eu.int

Ph.Eur. monographs

1. General notices:

An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph

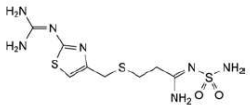
… however….

An enhanced approach to quality control could utilise process analytical technology (PAT) […] strategies as alternatives to end-product testing alone.

04/2013:1012

FAMOTIDINE

Famotidinum



$C_8H_{15}N_7O_2S_3$ M_r 337.4
[76824-35-6]

DEFINITION

3-[[[2-[(Diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]-*N*′-sulfamoylpropanimidamide.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or yellowish-white, crystalline powder or crystals.

Solubility: very slightly soluble in water, freely soluble in glacial acetic acid, very slightly soluble in anhydrous ethanol, practically insoluble in ethyl acetate. It dissolves in dilute mineral acids.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *famotidine CRS*.

If the spectra obtained show differences, suspend 0.10 g of the substance to be examined and 0.10 g of the reference substance separately in 5 mL of *water R*. Heat to boiling and allow to cool, scratching the wall of the tube with a glass rod to initiate crystallisation. Filter, wash the crystals with 2 mL of iced *water R* and dry in an oven at 80 °C at a pressure not exceeding 670 Pa for 1 h. Record new spectra using the residues.

TESTS

Appearance of solution. Dissolve 0.20 g in a 50 g/L solution of *hydrochloric acid R*, heating to 40 °C if necessary, and dilute to 20 mL with the same acid. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 12.5 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dissolve 2.5 mg of *famotidine impurity D CRS* in *methanol R* and dilute to 10.0 mL with the same solvent. To 1.0 mL of the solution add 0.50 mL of the test solution and dilute to 100.0 mL with mobile phase A.

Reference solution (c). Dissolve 5.0 mg of *famotidine for system suitability CRS* (containing impurities A, B, C, D, F and G) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 50 °C.

Mobile phase:

- *mobile phase A*: mix 6 volumes of *methanol R*, 94 volumes of *acetonitrile R* and 900 volumes of a 1.882 g/L solution of *sodium hexanesulfonate R* previously adjusted to pH 3.5 with *acetic acid R*;
- *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 23	100 → 96	0 → 4	1
23 - 27	96	4	1 → 2
27 - 47	96 → 78	4 → 22	2

Detection: spectrophotometer at 265 nm.

Injection: 20 µL.

Identification of impurities: use the chromatogram supplied with *famotidine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, F and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention with reference to famotidine (retention time = about 21 min): impurity D = about 1.1; impurity C = about 1.2; impurity G = about 1.4; impurity F = about 1.5; impurity A = about 1.6; impurity B = about 2.0.

System suitability:

- *retention time*: famotidine = 19-23 min in all the chromatograms;
- *resolution*: minimum 3.5 between the peaks due to famotidine and impurity D in the chromatogram obtained with reference solution (b).

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.5; impurity C = 1.9; impurity F = 1.7; impurity G = 1.4;
- *impurities C, D*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *impurities A, B, F, G*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Solvent mixture: *dimethylformamide R*, *water R* (30:70 *V/V*).

0.5 g complies with test H. Prepare the reference solution using 0.5 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C at a pressure not exceeding 670 Pa for 5 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.120 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

Ph.Eur. General notices

“The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its **design**, together with its **control strategy** and data derived, for example, from **validation studies** of the manufacturing process.“

"Real-time release testing […] is not precluded by the need to comply with the Pharmacopoeia”

Ph.Eur. 5.15 Functionality-related characteristics

- FRC sections are non-mandatory
- FRCs are not exhaustive, but typical for the excipient:
  - Particle size distribution
  - Powder flow
  - Bulk and tapped density
  - Viscosity
  - Melting point

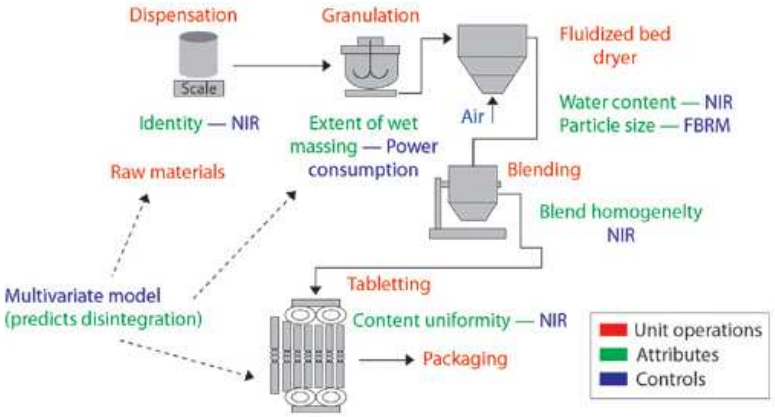
"Knowledge of FRCs may facilitate the application of process analytical technology (PAT)"

EMA Guideline on Real Time Release Testing (2012)

An appropriate combination of

- process controls (CPP) and
- pre-defined material attributes

may provide greater assurance of product quality than end-product testing



Demonstrating end-product quality by PAT/ QbD

The use of PAT analytical methods to demonstrate product quality is fully in line with the requirements and expectations of Ph.Eur., ICH and EMA Guidelines

Ph.Eur. 2.9.40/ USP 905: Understanding the UDU test

- Sample 30 units
- N = 10, calculate acceptance value

$$AV = \left| M - \overline{X} \right| + ks$$

- OK if AV ≤ L1

…or else: N = 30

- AV ≤ L1
- No unit outside M L2/100

Variable	Definition	Conditions	Value
	as a percentage of the label claim		
n	Sample size (number of dosage units in a sample)		
k	Acceptability constant	If n = 10, then	2.4
		If n = 30, then	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(x_i - \overline{X})^2}{n-1}\right]^{1/2}$
RSD	Relative standard deviation		$\frac{100s}{\overline{X}}$
M (case 1) To be applied when $T \leq 101.5$	Reference value	If 98.5 per cent ≤ $\overline{X}$ ≤ 101.5 per cent, then	$M = \overline{X}$ ($AV = ks$)
		If $\overline{X}$ < 98.5 per cent, then	M = 98.5 per cent (AV = 98.5 − $\overline{X}$ + ks)
		If $\overline{X}$ > 101.5 per cent, then	M = 101.5 per cent ($AV = \overline{X}$ − 101.5 + ks)
M (case 2) To be applied when $T > 101.5$	Reference value	If 98.5 per cent ≤ $\overline{X} \leq T$, then	$M = \overline{X}$ ($AV = ks$)
		If $\overline{X}$ < 98.5 per cent, then	M = 98.5 per cent (AV = 98.5 − $\overline{X}$ + ks)
		If $\overline{X} > T$, then	$M = T$ per cent ($AV = \overline{X} - T + ks$)
Acceptance value (AV)			General formula: $\lvert M - \overline{X} \rvert + ks$ Calculations are specified above for the different cases.
$L1$	Maximum allowed acceptance value		$L1$ = 15.0 unless otherwise specified
$L2$	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than 0.75 M while on the high side, no dosage unit result can be greater than 1.25 M (This is based on $L2$ value of 25.0)	$L2$ = 25.0 unless otherwise specified
T	Target content per dosage unit at time of manufacture, expressed as a percentage of the label claim. Unless otherwise stated, T is equal to 100 per cent or T is the manufacturer's approved target		

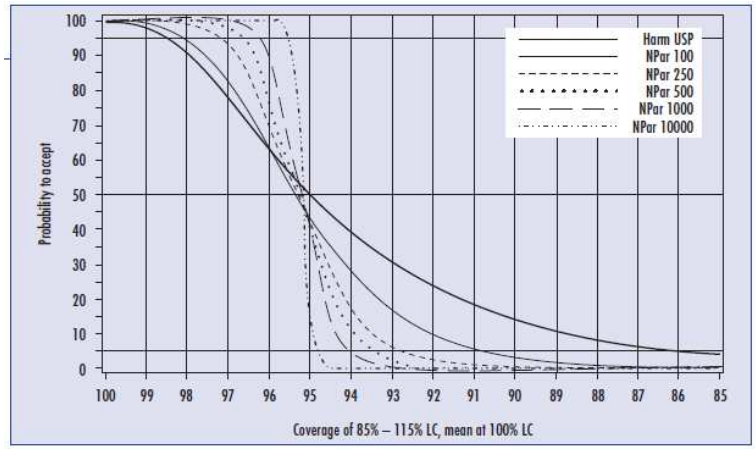
Uniformity of dosage units – regulatory aspect

- The UDU test is mandatory, e.g. for unit dose products
- The European Pharmacopeia allows alternative testing

- Individual applications:
  - Industry requested alternative test for dosage uniformity using large samples
  - Much work on both sides
  - Case-to-case decisions

Background: Large N issue

Dennis Sandell, et al. Drug Information Journal 40 (2006) 337ff



Dennis Sandell, PhD
PhRMA CM&C Statistics Expert Team, AstraZeneca, Lund, Sweden

Kim Vukovinsky
PhRMA CM&C Statistics Expert Team, Pfizer, Groton, Connecticut

Myron Dionor
PhRMA CM&C Statistics Expert Team, sanofi aventis Group, Kansas City, Missouri

Jeff Hofer
PhRMA CM&C Statistics Expert Team, Eli Lilly and Company, Indianapolis, Indiana

James Pazdan
PhRMA CM&C Statistics Expert Team, Novartis, East Hanover, New Jersey

Joop Timmermans, PhD
PhRMA PAT Expert Team, Pfizer, Morris Plains, New Jersey

Key Words
Process analytical technology (PAT); Uniformity of

Development of a Content Uniformity Test Suitable for Large Sample Sizes

Applications of process analytical technology (PAT) are currently attracting wide interest. One of the potential applications of PAT is large-scale (hundreds or thousands of tablets), real-time evaluation of tablet content uniformity. An issue associated with this situation is which acceptance criteria the obtained large sample should meet. Traditionally, a sample of 10–30 tablets is assessed against criteria specified in the harmonized pharmacopeial specification for uniformity of dosage units (UDU). These criteria, however, are not directly applicable to large sample sizes as application of the acceptance criteria in the harmonized pharmacopeial specification in these situations results in an overly restrictive requirement. Industry has highlighted this issue as a potential deterrent for extended applications of PAT in this area. A one-tiered counting test for UDU with associated acceptance criteria is proposed as an alternative to the harmonized pharmacopeial specification for UDU. The proposed test is applicable to large sample sizes yet provides the same assurance of uniformity of the batch as the harmonized pharmacopeial specification.

INTRODUCTION

Applications of process analytical technology (PAT) are currently attracting wide interest from

fies (among other requirements; see below) that no result outside 75%–125% is allowed in the sample. This requirement may be reasonable when small sample sizes (in the range 10–30 units) are inspected using traditional methodology but is counterproductive in applications such as PAT, for which a much larger sample from the batch usually is assessed. Given these large sample sizes, characterized using near infrared (or similar) methods, occasional results outside the 75%–125% limits could be observed without necessarily indicating substandard uni-

Acceptance Limit of Proposed Test for a Selection of Sample Sizes

n	100	250	500	750	1,000	2,000	3,000	4,000	5,000	10,000
c	4	11	23	35	47	95	143	191	239	479

Uniformity of dosage units using large sample sizes

- 2008: Efpia request to the European Medicines Agency (EMA):

The pharmacopeia should not represent a barrier/ disincentive to the implementation of PAT

- Specific issues raised for large N on the UDU test (Ph.Eur. 2.9.40):
  - Rigid requirement: no single unit outside +/- 25 % (if L2 = 25)
    When n >> 30, one or few largely deviating units is expected
  - Improved batch knowledge with large sample not appreciated

- EDQM PAT WP was established on request of the EMA PAT team
  - Revision of UDU test and other general chapters (NIR, Raman)

Ph.Eur. 2.9.47

Option 1

- Parametric

$$AV = \left| M - \overline{X} \right| + ks$$

Depending on sample size:

Limit for number of units outside $(1 \pm L2 \times 0.01)T$: **c2**

n (≥)	k	c2
100	2.15	0
105	2.16	
120	2.17	
139	2.18	
161	2.19	
176	2.19	1
189	2.20	
224	2.21	
270	2.22	
280	2.22	2
328	2.23	
385	2.23	
407	2.24	
490	2.24	

Option 2

- Non-parametric

Depending on sample size:

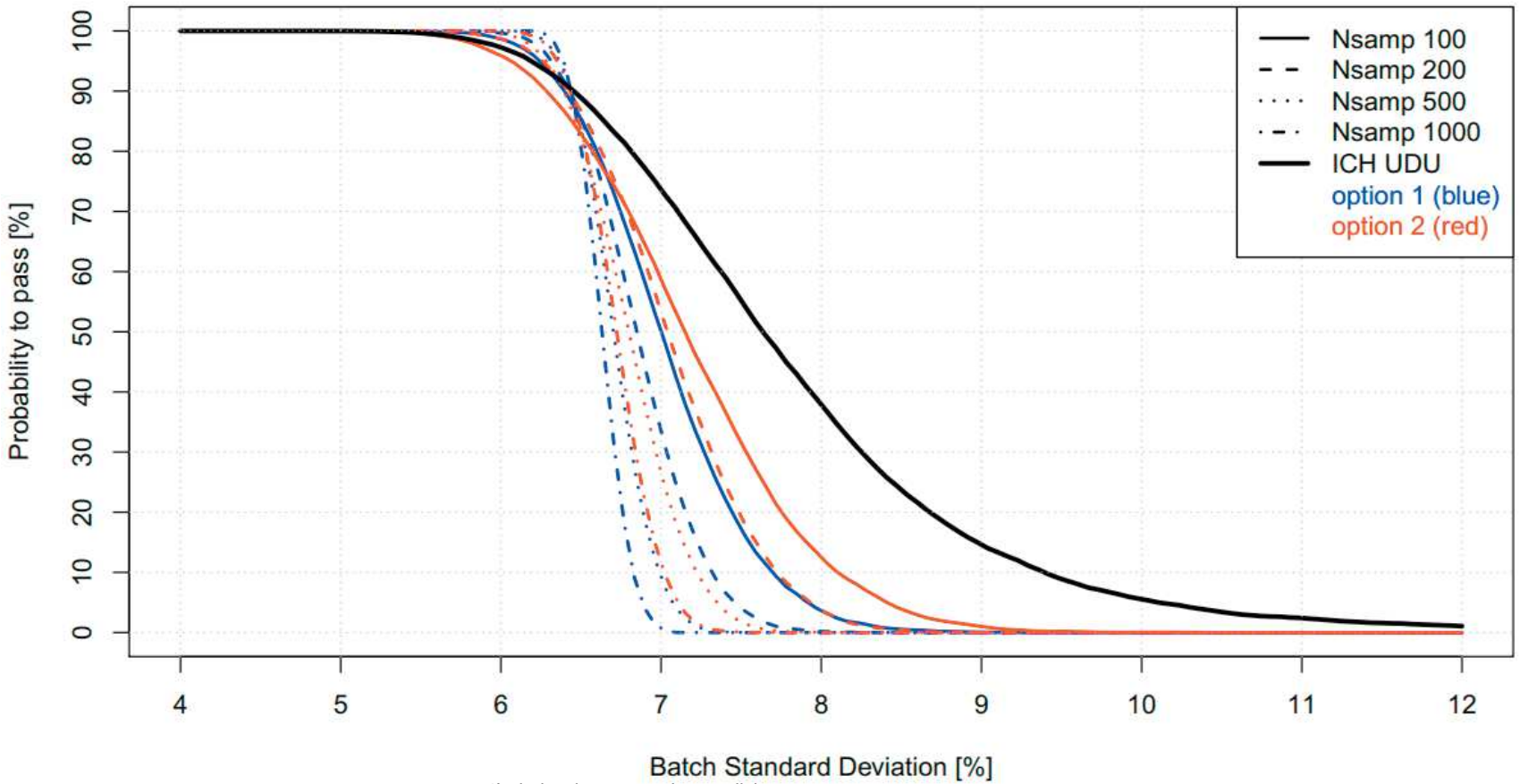
Limit for number of units outside $(1 \pm L1 \times 0.01)T$: **c1**

$(1 \pm L2 \times 0.01)T$: **c2**

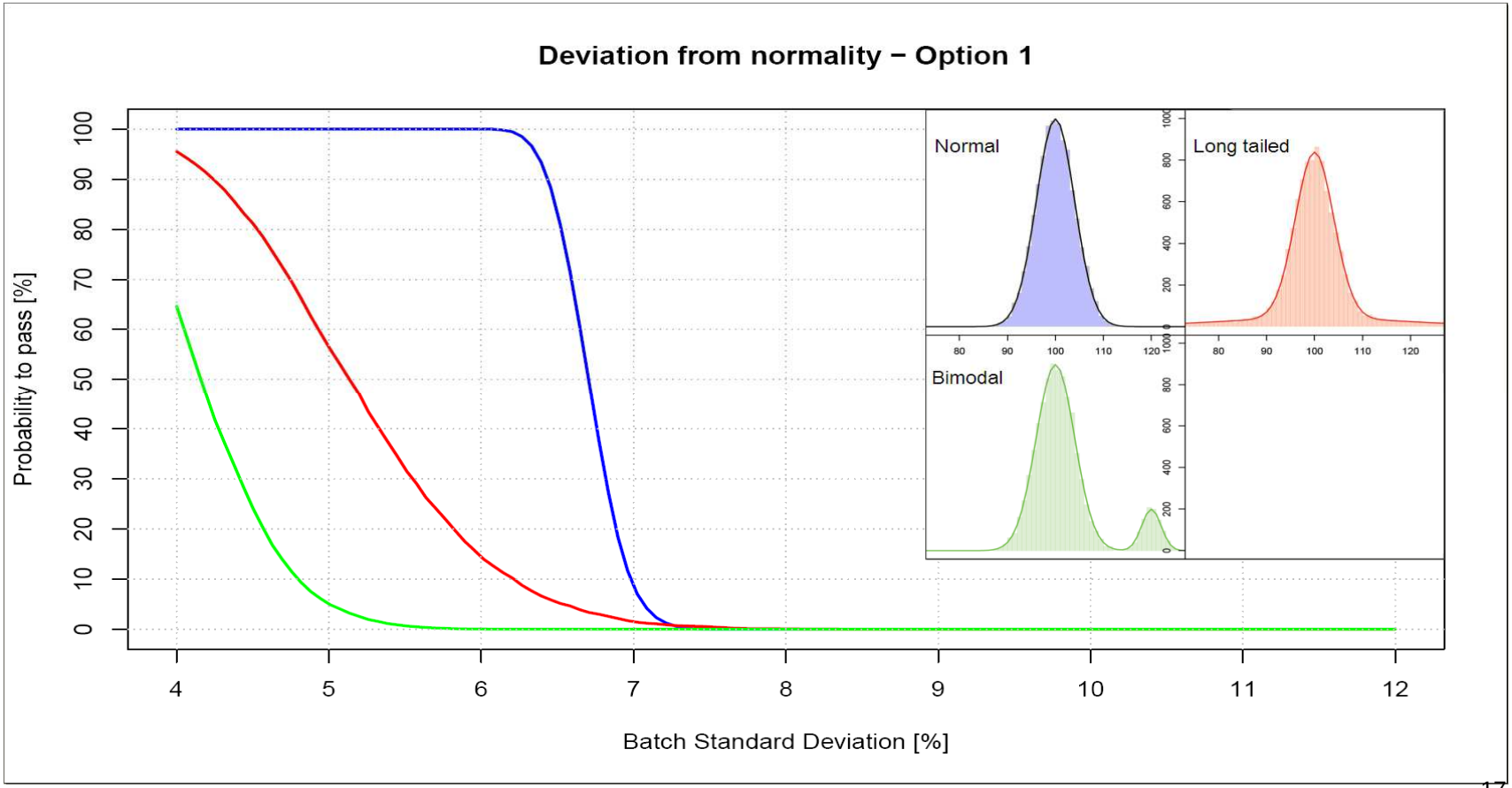
n (≥)	c1	c2
100	3	0
123	4	
159	5	
176	5	1
196	6	
234	7	
273	8	
280	8	2
313	9	
353	10	
385	10	3
394	11	
434	12	
476	13	
490	13	4
517	14	
543	15	
594	15	

~90 % probability to pass Ph.Eur. 2.9.40 on any small sample

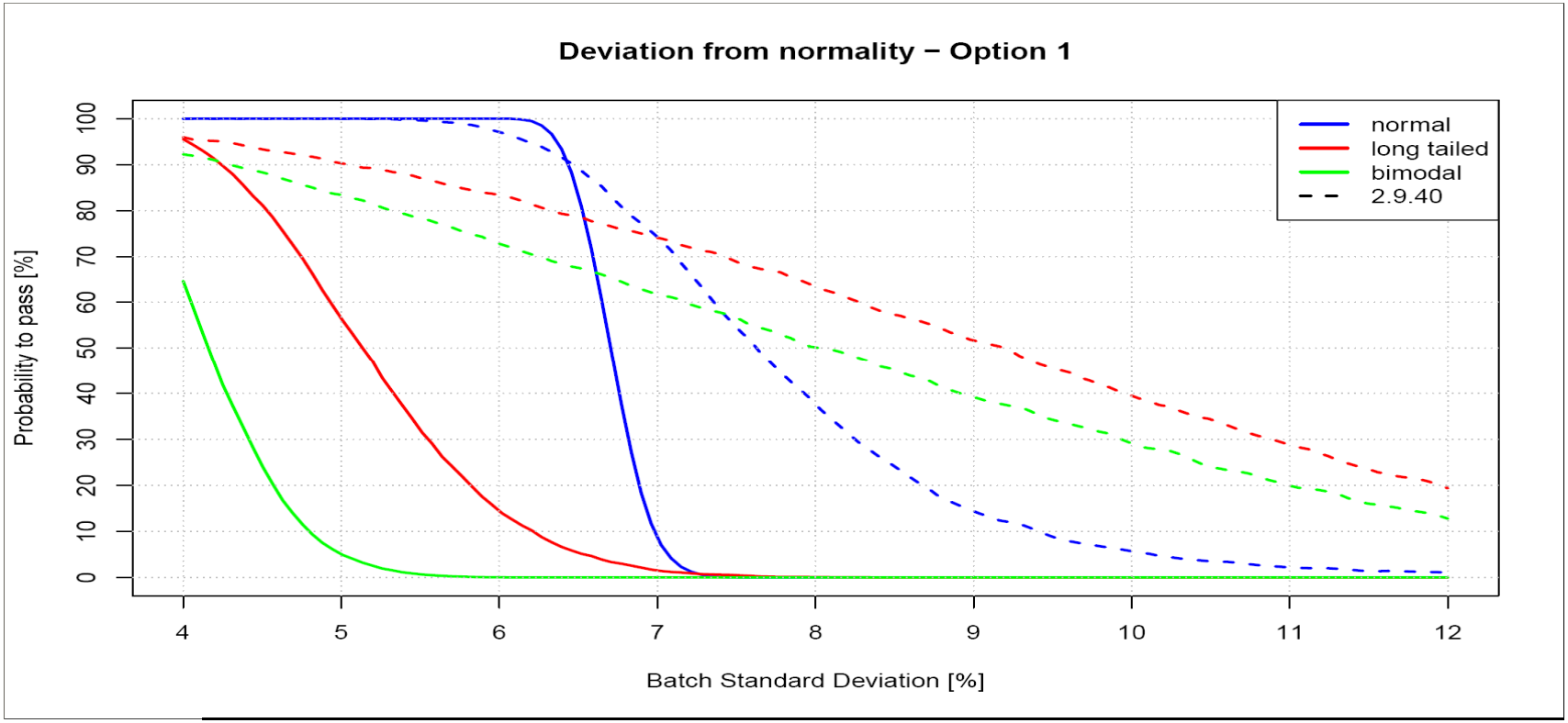
Probability to pass Ph.Eur. 2.9.40/ 2.9.47 (N 100 - 1,000)



Probability to pass Ph.Eur. 2.9.47 (N=500)



Comparison of 2.9.40 and 2.9.47



Reference: Ø. Holte and M. Horvat 2012. Pharm Sci Technol 36(10): 118-122.

PAT analytical methods – opportunities and pitfalls

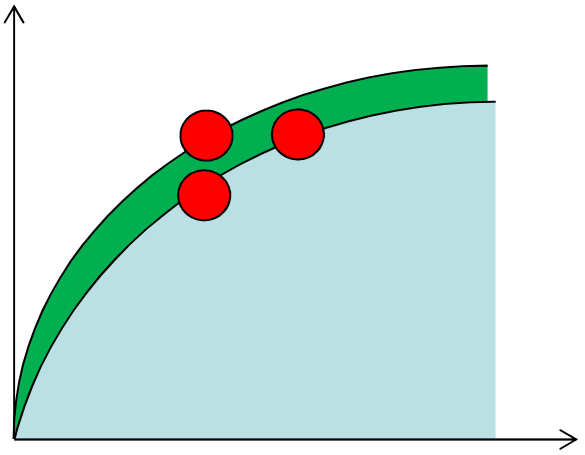
Opportunities:

- Process control, demonstration of quality (RTR testing)
- Increasing yield
- Optimising process times
- process knowledge (Life cycle management)

Pitfalls

- Missing link from the PAT result to the quality standard/ CQA
- Black box-approach to PAT
- Choice of material attribute (range)
- Maintenance/ cleaning/ replacement of equipment
- Different set up between manufacutring sites?
- Plan B in case of
  - equipment failure
  - result outside validated range (library)

Link from PAT to quality standard



- Requirement = test method + limit
- Example dissolution:

Q **70%/ 20** min vs. Q **80%/ 30** min

Q80%: **30 min/ 50 rpm** vs. **20 min/ 100 rpm**

PAT example:

Diss. = tablet hardness **x** exact excipient comp. **x** API particle size

- RTR testing (PAT): surrogate for the in vitro dissolution test
- In vitro dissolution: surrogate for in vivo performance (PK biobatch)

Link from PAT to quality standard

- Example: Assay + dose uniformity
- PAT approach: NIR spectroscopy + tablet weight

Pros:

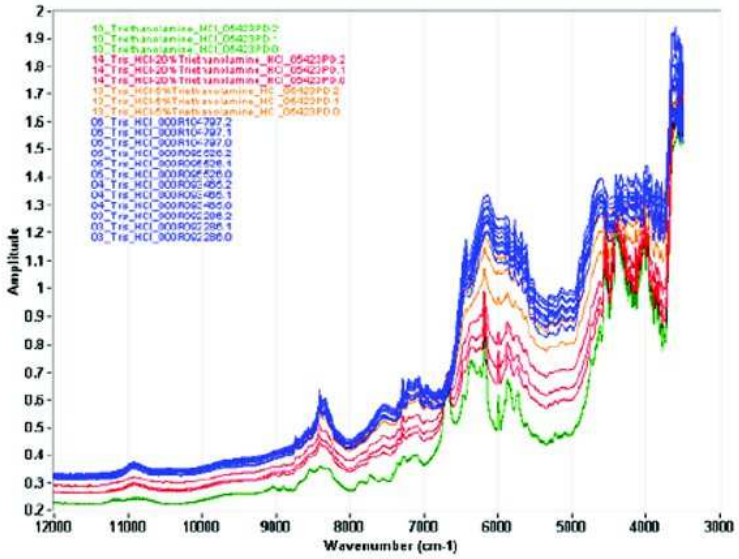
- Large sample size: result more representative for the batch
- Immediate results:
  - RTR testing
  - Feed-back/ feed-forward controls possible

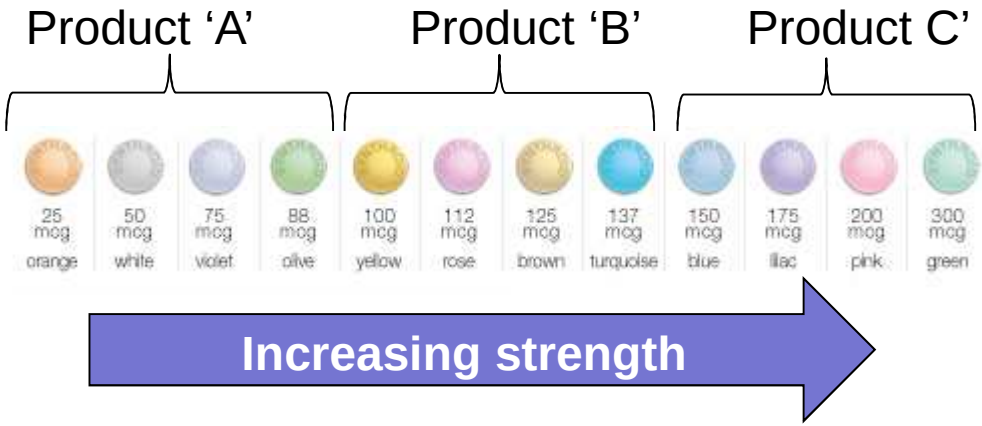
Cons:

- Concentration of active (NIRs) and unit weight determined on different units
- Accuracy/ precision for NIRs typically lower than e.g. UV

Black box approach

- Relate spectral variability to relevant material attribute!
- Method performance is highly dependent on:
  - the composition of library
  - the algorithm



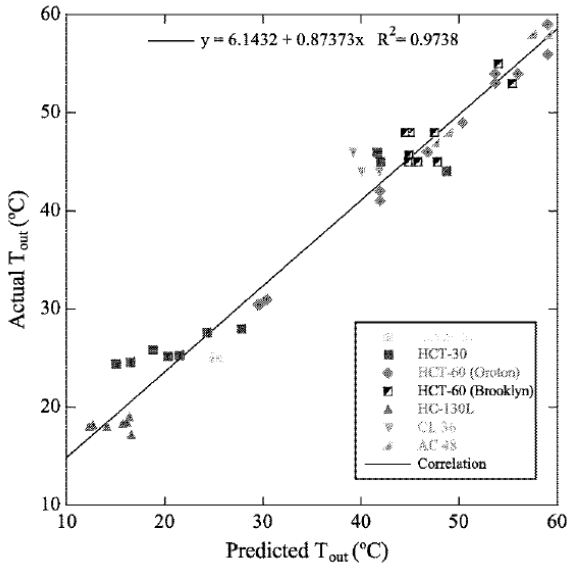


Purpose of the method:

- Assay?
- Identity?

Choice of relevant material attribute

- Purpose of model:
  Controlling film coating



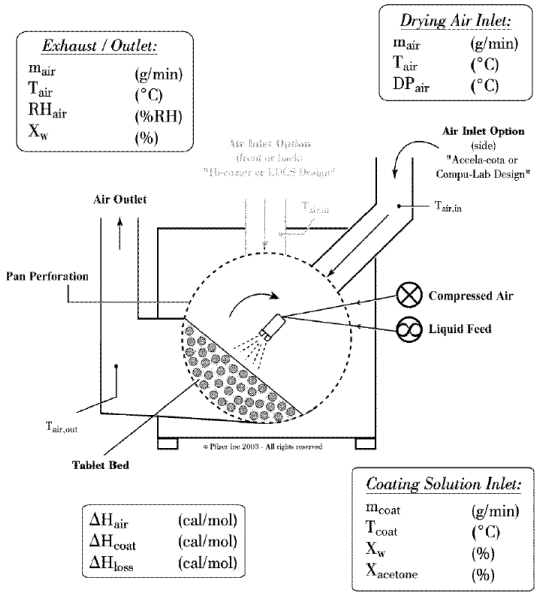


Figure 1. Schematic representation of the film-coating process flow diagram for side-vented coating pans.

Great correlation, but is T_{out} relevant for CQA (film coating)?

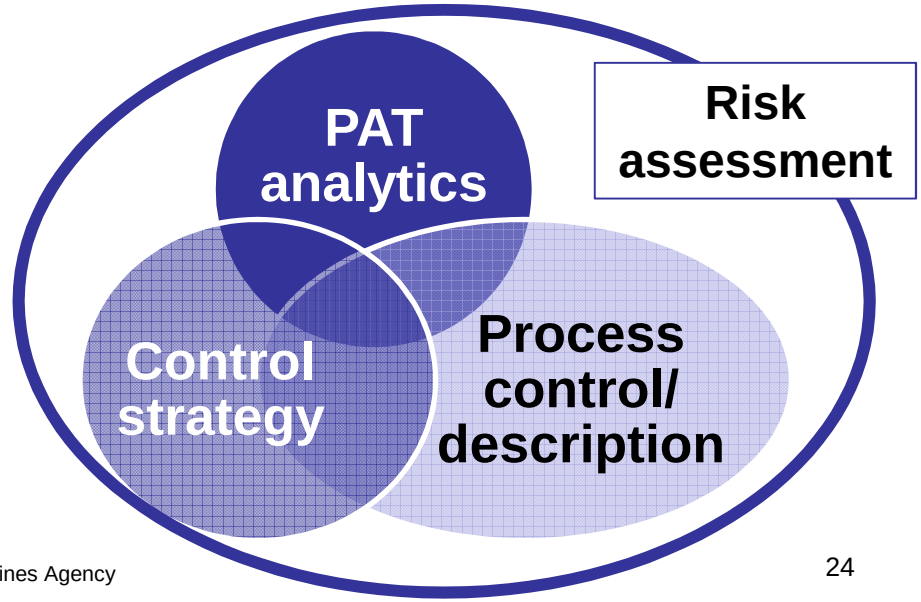
PAT in the dossier - where, what and how much?

Where

- CTD module S.4/ P.5
- Often relevant for PAT: Analytical method integrated part of development: cross-references to other parts of the dossier

What:

- Description and validation
- Link to CQA (S.2.6/ P.2 ?)



QbD in the dossier - where, what and how much?

- The level of details presented should commensurate with the impact of the result
- Purpose of PAT:
  - development/ process exploration/ monitoring?
  - Real time release testing?
- Sufficient data to allow a critical assessment
- Sufficient data/ discussion to follow the logics of the development work and agree on the control strategy

- Quantity of text = Quality of message? (No…)

Summary

- The manufacturer must assure his product complies with quality standards laid down in the pharamcopoeia and guidelines
- Quality requirements apply regardless of control strategy

- QbD/ PAT is one way of demonstrating quality
- This approach is fully in line with current regulatory practice
  - Ph.Eur., Guidelines, Specific case histories
- Dossier requirements: sufficient for third party review