New and revised General Chapters in the European Pharmacopoeia

Workshop New Technologies

European Pharmacopoeia 9th Edition

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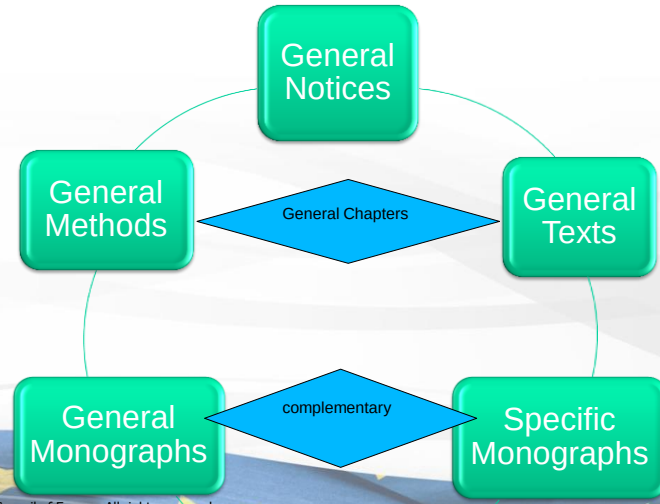
European Pharmacopoeia Department

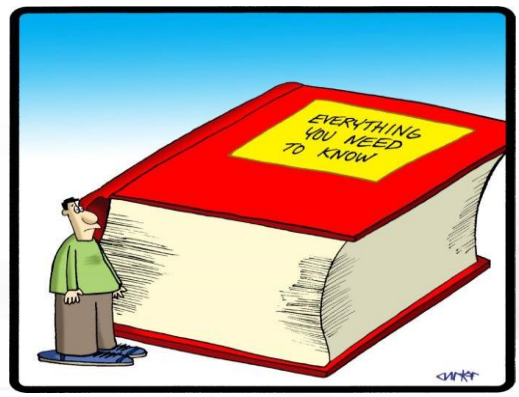
Content of the presentation

- ❑ General information about General Chapters
- ❑ Modernisation program
- ❑ Template
- ❑ Examples

Which type of texts you find in the European Pharmacopoeia



General Chapters



Quiz:

- Is the use of a general chapter (analytical procedure) mandatory?
- Are alternative methods allowed?
- Do general methods require validation by the user?

General chapters: why and how to use

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can also be used where there is no monograph
- Provide general requirements for equipment, equipment qualification or calibration
- Provide general requirements for system suitability tests

General chapters: why and how to use

- Not mandatory **"*per se*"**
- When referred to in a monograph, they become part of the standard, i. e. ***mandatory***:
- Example: *IR spectrophotometry 2.2.24*, Monograph Irbesartan supplement 8.8:

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: irbesartan CRS

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness at 60 °C and record new spectra using the residues

General chapters: why and how to use

- Some general chapters are not referred to in any monograph (Raman spectrometry, revised in 2015)

Useful guidance, can be referred to in applications

Other examples:

- *Chemometric methods applied to analytical data 5.21*, published in supplement 8.7
- *Reference Standards 5.12*

Modernisation Program

- ✓ « Internal » harmonisation using a template
- ✓ To include recent techniques and produce a Pharmacopoeia which is scientifically state-of-the-art
- ✓ To improve existing methods to take into account recent progress in analytical technology and regulatory practice
- ✓ To suppress toxic reagents or materials
- ✓ To introduce and/or improve elements of equipment performance and qualification -> be more user-friendly
- ✓ To introduce and/or improve general system suitability tests
- ✓ International harmonisation within PDG (Pharmacopoeial Discussion Group)

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Template

Principle of the analytical technique (high level)

- Short introduction including useful and summarised information, not necessary to include extensive theoretical information that can be found in standard texts on the subject. (A publication of additional information in Scientific Notes may be considered in parallel)
- Glossary, definitions

Equipment

- Description: components of the equipment

Equipment performance

- Minimum requirements for performance
- Elements of qualification (degree of detail on a case by case basis)
- System suitability (general requirement in the method unless otherwise prescribed in the monograph)
- Performance checks before use

Template

Procedure

- Operation of the equipment: including adjustment (calibration) if relevant
- Test method: preparation of samples/standards/reagents if relevant
- Calculation of test results and statistics if relevant

Validation requirements

This section would be added where validation requirements differ from those given in ICH Q2 or if more information than just Q2 is given or different extent (i.e. other validation characteristics than recommended in ICH Q2).

Where relevant, in particular for quantitative applications, acceptance criteria are given.

Additional information (technical state of the art)

In exceptional cases, e.g. environmental and safety factors, special operating conditions

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Technical improvement or new methods

Examples:

- Chemometrics and chemical imaging, 5.21 and 5.24
- IR absorption spectrophotometry 2.2.24: *under revision, will take account of increased importance of ATR technique*
- Raman spectrometry 2.2.48, Ph. Eur. 8.7: *more detailed description of qualitative and quantitative analysis, description of new devices, e. g. hand-held spectrometers, new reference standards for qualification*
- Melting point, 2.2.14, Ph. Eur. 9.1*: combines previous 2.2.14 and 2.2.60 (instrumental method), takes account of equipment used and equipment no longer available, new SST*

Technical improvement or new methods

Examples:

- Potentiometric determination of pH, 2.2.3, Ph. Eur. 8.8: *use of commercially available certified reference buffers, take account of the use of recent pH-meters*
- High performance TLC, 2.8.25, Ph. Eur. 9.0: *qualitative use for herbal drugs and preparations, better selectivity, new system suitability tests*
- Absorption spectrophotometry, ultraviolet and visible, 2.2.25, Pharmeuropa: *inclusion of UV-detectors in chromatography, inclusion of different measurement modes, like diffuse reflection mode, recent equipment described, PAT application included*

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Replacement of toxic reagents and materials

Examples:

- *Replacement of potassium dichromate in the control of absorbance in* UV-VIS spectrophotometry, 2.2.25
- *Replacement of mercury containing thermometers* (2.2.11, 2.2.12 drop point, boiling point, 2.2.16 melting point-instantaneous method), *electrodes* (2.2.3, potentiometric determination of pH, 2.2.19 amperometric titration) and *reagents* (4.22 volumetric solutions) in several general chapters.

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- ✓ To introduce and/or improve elements of equipment performance and qualification -> be more user-friendly, increased flexibility
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Equipment performance and -qualification

- DQ, IQ, OQ and PQ represent an important aspect in the QMS (quality management systems) of modern laboratories: many general chapters refer to minimum requirements of qualification

Details, like frequency of PQ, remain in the responsibility of the user!

Equipment performance, -qualification and calibration

Examples:

- 2.2.14 Melting point :

Qualification/calibration is performed using 2 certified reference materials which are selected to cover the temperature range used on the equipment

- 2.2.3 Potentiometric determination of pH:

Calibration is performed using commercially available certified reference buffers

- 2.2.25 UV-Vis spectrophotometry

Qualification is performed by controlling wavelength and absorbance accuracy, photometric linearity, stray light and control of resolution

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General system suitability tests

Note: System suitability tests in general chapters are complementary to specific monographs

Examples:

- ➢ Melting point: System suitability test is performed before the measurements by choosing a suitable reference material with a melting point close to that expected for the substance to be examined
- ➢ UV-VIS: System suitability tests, such as wavelength control, absorbance, stray light, are different depending on the use of the test, i. e. qualitative or quantitative

General system suitability tests

- Chromatographic separation techniques: SSTs include symmetry factor (0.8 to 1.5), minimum S/N ratio of 10 at the quantification limit, repeatability requirement in chromatographic assays

To be performed in addition to the specific tests in the monograph, such as resolution, peak-to-valley ratio etc

Under revision: SSTs and adjustments of chromatographic conditions will change!

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PDG programme

Some general methods are on the work program of the Pharmacopoeial Discussion Group (PDG)

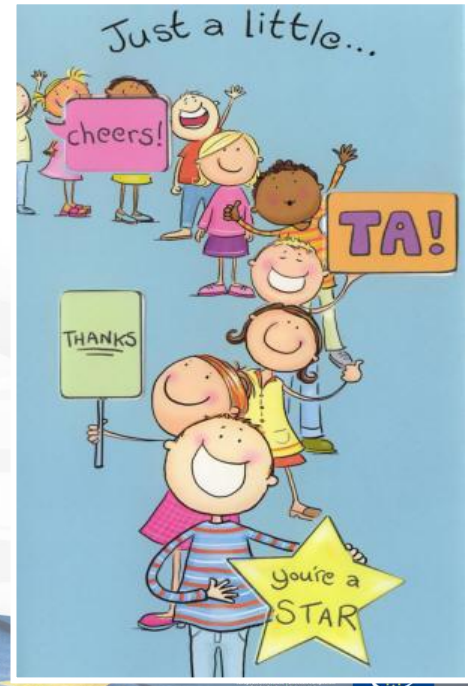
- Example Thermal analysis, 2.2.34: published in suppl. 8.6
- Example Metal impurities: strives to harmonise the testing for elemental impurities in context with Q3D, currently chapter 2.2.24 in Ph. Eur.
- Example Chromatography: strives to harmonise definitions, SST-requirements (resolution), permitted adjustments of chromatographic conditions:

  e. g. Switch from HPLC to UHPLC ?

Conclusion

- The structure of general chapters will be harmonised (template) as far as possible and appropriate
- Reagular review and modernisation are necessary to remain scientifically state-of-the-art
- New measurement techniques and equipment have to be taken into account
- Follow the wish of users to give more advice (equipment qualification) whilst increasing the flexibility of the texts

Thank you for spending time with me!



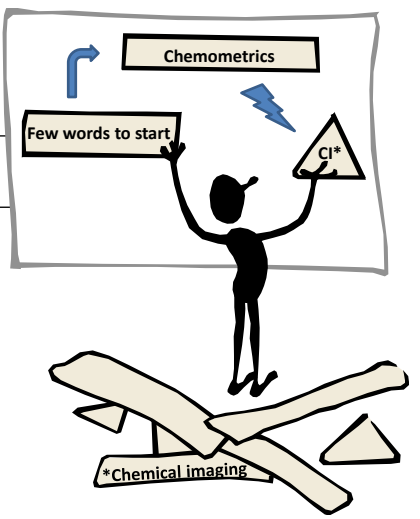
Chemometrics
and
Chemical imaging

Michel Ulmschneider
VSADM PAT MG

Few words to start

Chemometrics

Chemical imaging



Spectroscopy	Description	On/in line	Chemical ID	Examples
Mid-infrared, near- infrared, and Raman spectroscopy	Vibrational spectroscopy	X	X	Reaction monitoring Polymorphism Content determination Process monitoring (drying, granulation, blending)
Hyperspectral imaging	Vibrational spectroscopy coupled with spatial analysis	X	X	Chemical compound distributions Counterfeit detection
UV-vis spectroscopy	Photoelectron spectroscopy	X	X	Color measurement Dissolution testing Cleaning validation (ppm-level detection)
Terahertz spectroscopy and imaging	Far infrared spectroscopy 3D imaging		X	Polymorphism Coating integrity and thickness API distribution
Laser Induced Breakdown Spectroscopy	Plasma generated by a laser pulse and detection of the emitted light (destruction of sample)		X	Drug development Process troubleshooting
Laser diffraction	Interaction of a laser beam with particles and detection of the scattered light	X		Particle size determination
Acoustic methods	Active or passive usage of sound echoes	X		Solid, semi-solid and high viscose sample High shear granulation monitoring Crystallisation monitoring

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Vibrational spectroscopy

	NIR	MIR	Raman
Spectral range (cm^{-1})	12 000-4000	4000-600	4000-50
Signal intensity	+	+++	+
Microscopic analysis	No	Yes	Yes
Fiber optic interfacing	Yes	Possible (limited length)	Yes
Sampling through glass	Yes	No	Yes
Qualitative application	Yes	Yes	Yes
Quantitative application	Yes	Difficult	Yes
Instrument robustness	++++	++	+++
Data interpretation	Chemometrics	Direct	Direct

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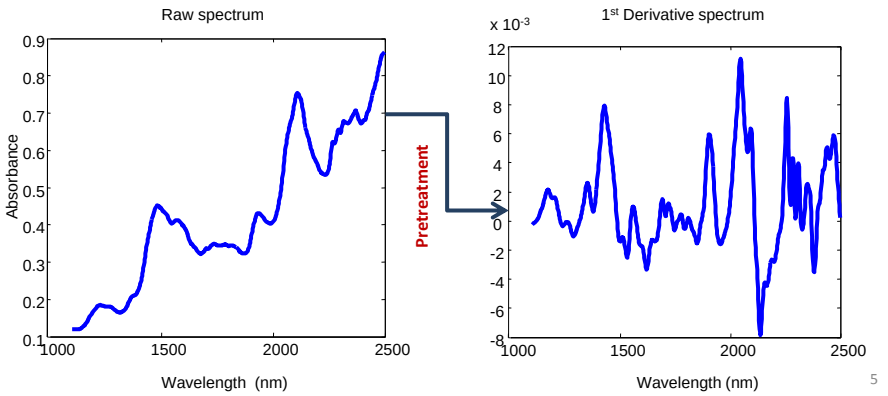
From the poor NIR signal…

Plus
- NIR radiation goes through glass
- Non-destructive
- Fast
- No or reduced sample preparation
- Spectrum includes chemical and physical information

Minus
- Spectra difficult to interpret
- Multivariate calibrations to extract latent information
- Calibration transfer between spectrometers



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…to practical applications like these…

Intact and rapid sample measurements for:

- **Confirmation** of identity
- e.g. container wise identification of excipients and APIs
- Confirmation of identity of formulated preparations for clinical trials
- **Quantitative determinations**, typical example being water content determination
- Process understanding
- **In-line, on-line, at-line analytics** in chemical and galenical facilities
- PAT

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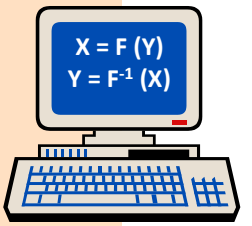
…we need chemometrics!

With NIR there is an information problem:

- Information is *scrambled*
- Direct interpretation is barely possible
- Technique requires large data sets
- Sensing physics **and** chemistry



Calibration i.e. modelling step is required !

Chemometrics for the design and analysis of data collections

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Few words to start

Chemometrics

Chemical imaging

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Chemometrics

A discipline which appeared in the early 70's

Chemometrics is a discipline that relies on mathematical, statistical, and other formal numerical methods together with computer science :

a) To extract maximum information by analyzing chemical data

b) To design or select optimal experimental procedures

c) To obtain knowledge about systems

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- Even if chemometrics relies on exact and formal mathematical techniques, in practice
  - **numerical computation** (i.e. algorithmics) and
  - **empirical modelling** remain central to the discipline
- From a historical perspective, chemometric methods were developped to explore and evaluate spectroscopic data to extract information from collections of near-IR spectra
- Meanwhile applicability of chemometrics has proven to be valuable for a wider panel of analytical techniques

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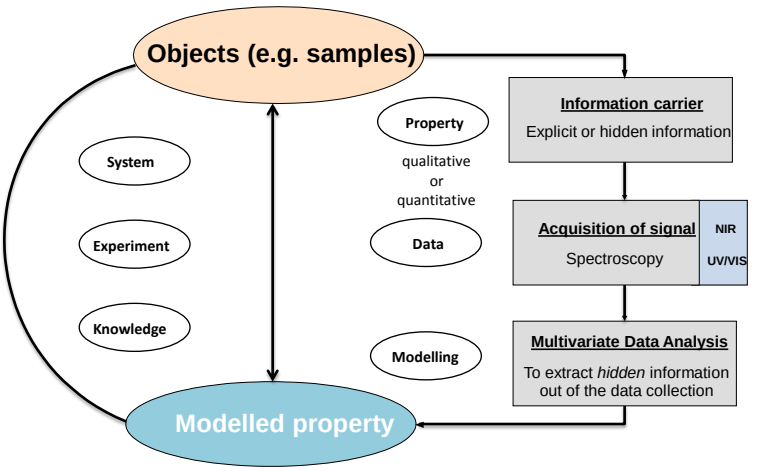
Illustration

Empirical modelling is central to chemometrics.



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Analysis of measurement tables
Non-linear PLS
Data mining
Operation research
Signal correction
Pharmacokinetic models
Data bases
Algorithmics
Signal filtering
Neural networks
Experimental design
Statistics
Analysis of variance
Pattern recognition
Process modelling
SIMCA
Expert systems
Signal processing
Curve resolution
Hierarchical classification
Discriminant analysis
Analysis of sensory data
Mixture design
Kalman filtering
Batch SPC
Factor analysis
Multivariate calibration
Data mining
Multivariate SPC
Sampling theory
Principal components
Cluster analysis
Control charts
K-nearest neighbors
Multiple and polynomial regression
"Omics" data analysis
Fractional factorial design
QSAR
Linear regression and calibration
Non-linear regression
Time series analysis
Information theory
Rules
Combinatorial chemistry
Method validation
Full factorial design
Image analysis
Genetic algorithms
Wavelet analysis
Signal compression

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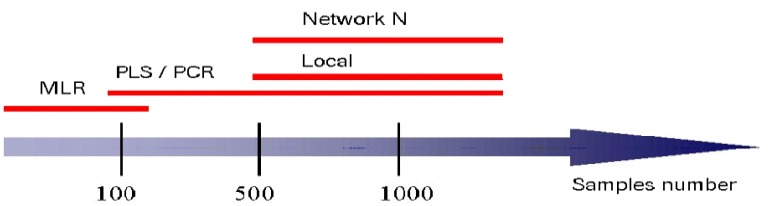
Selection of modelling techniques is not limited

However, there are some constraining parameters



- Complexity of algorithms
- Availability of samples that cover the expected variations of quality or value range
- Specificity and selectivity
- Robustness

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PCA and PLS are mainstream methods

Data analysis by projection

- Deal with the dimensionality problem
- Handle all types of multivariate data tables
- Compatible with collinearity, missing data, etc.
- Robust to noise in variables and responses
- Extract information from all data simultaneously
- Model relation between X and Y (PLS)
- Iterative algorithms

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Typically, at the beginning of a multivariate data analysis there is a data table with large dimensions and a hidden structure : many variables, many observations, all mixed up.

$$\mathbf{X} = \begin{pmatrix} x_{11}\ x_{12}\ x_{13}\ \ldots\ x_{1k} \\ x_{21}\ x_{22}\ x_{23}\ \ldots\ x_{2k} \\ \textbf{spectrum} \\ \ldots \\ \ldots\ x_{ij} \ldots \\ x_{n1}\ x_{n2}\ x_{n3}\ \ldots\ x_{nk} \end{pmatrix}$$

n samples

k wavelengths

x_{ij} absorbance

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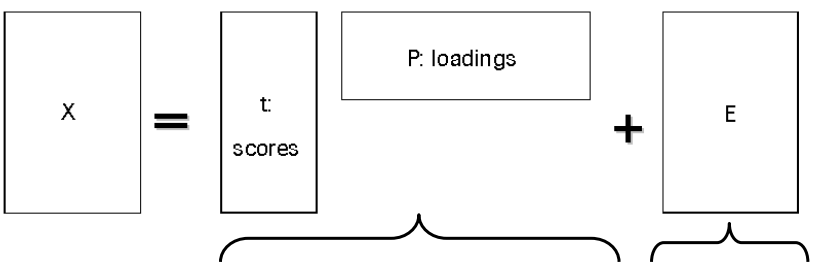
Principal Component Analysis

PCA is matrix algebra applied to a data table



DATA = STRUCTURED PART + ERROR

$$X = t_1 p'_1 + t_2 p'_2 + \ldots + t_k p'_k + E$$

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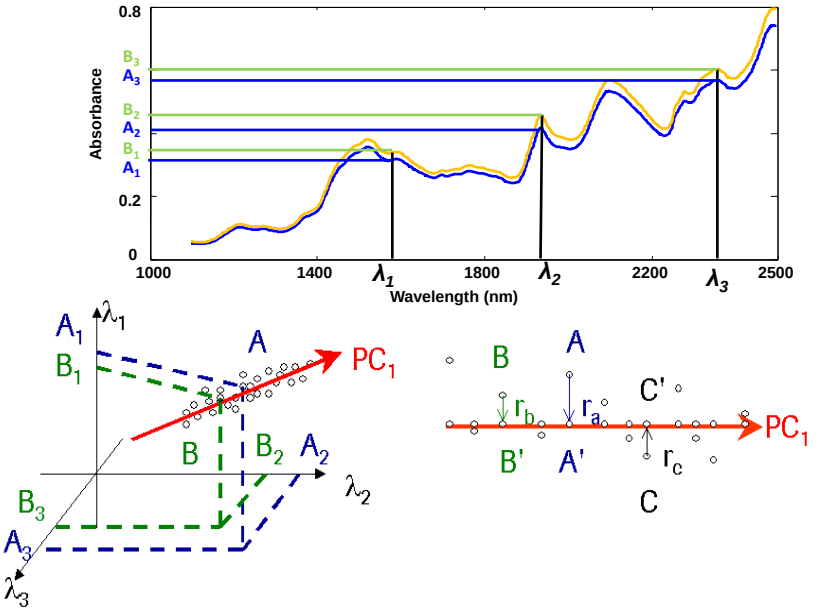

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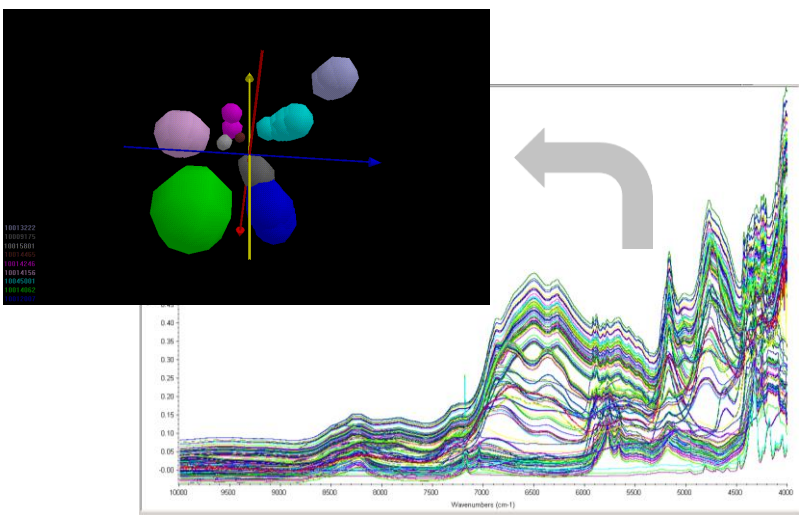
Principal Component Analysis

PCA to discriminate compounds



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Chemometric methods applied to analytical data (5.21)

- Has been published in Supplement 8.7 and entered into force on 1st April 2016
- The European Pharmacopoiea is first in including a chapter on chemometrics
- General chapter, for information only
- Provides a general introduction to the use of chemometric methods

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- The chapter supports data analysis in
  - Laboratory analytics
  - In-, on-line analytics
  - PAT
  - QbD
  - Process data mining
  - Big data
- Methods apply to *any* kind of data collection although a spectroscopic background could be detected

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- Features well established i.e. most used techniques
- Proposes PCA, SIMCA, MCR, MLR, PCR, PLS, SVM, and ANNs
- Brief description of principles
- Selection of methods is given without corresponding numerical algorithms
- Introduction of notations and formulas for information

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- There are recommendations for good practice
  - Implementation steps
  - Considerations on data
  - Considerations on applicability and scope
  - Typical characteristics
  - Limitations
- Glossary to rationalize wording

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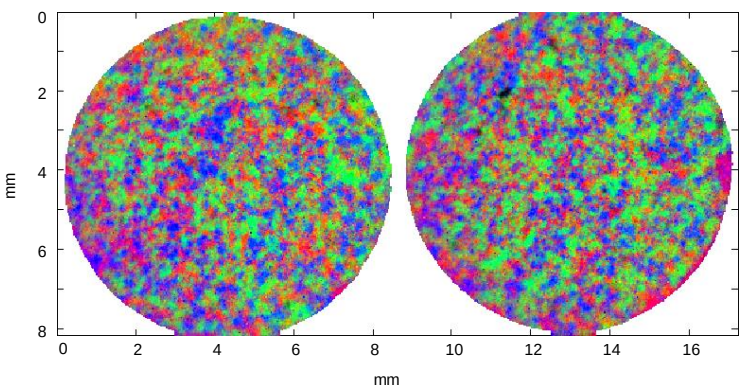
Few words to start

Chemometrics

Chemical imaging

2D chemical images



For which purpose chemical imaging?

- Trouble shooting
- Particle determination in solids
- Qualitative comparison of materials
- Estimation of galenical properties
- Homogeneity
- End-point assessment
- Counterfeits

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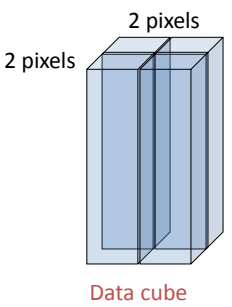
Usual method for producing 2D-images



Example

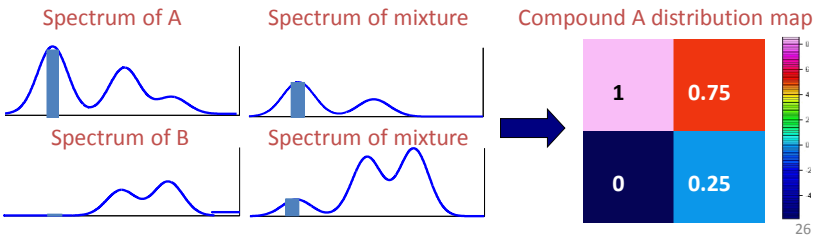
- Sample analysis on 4 pixels
- 2 compounds (*A and B*)

Extraction of compound A distribution map

1- From reference spectra : selection of a specific spectral range for A.

2- From mixture spectra : integration on the selected spectral range (area considered as a concentration estimation).

3- Map extraction : color coding from concentration estimations.



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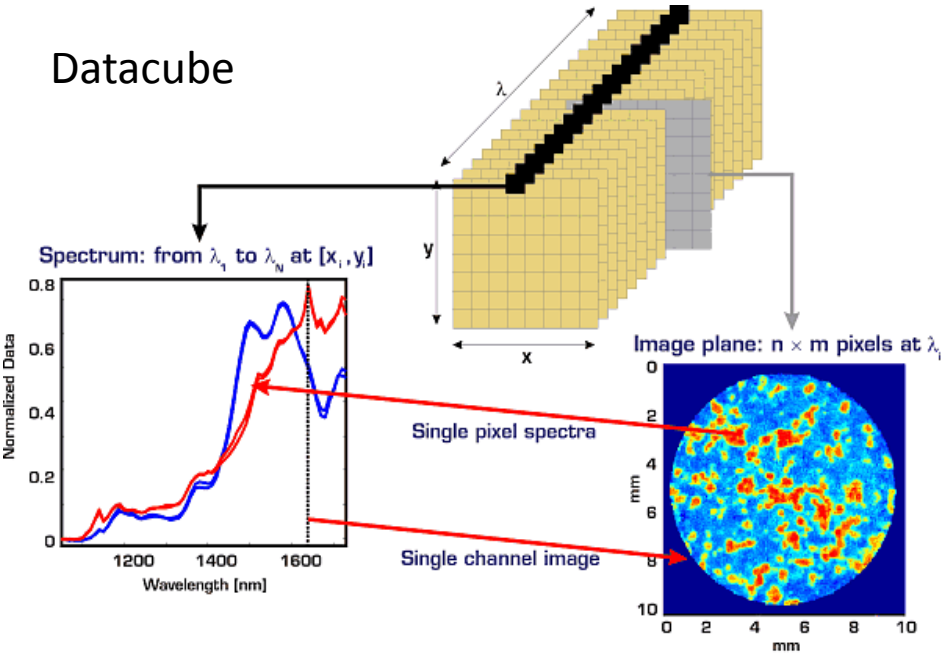
Datacube



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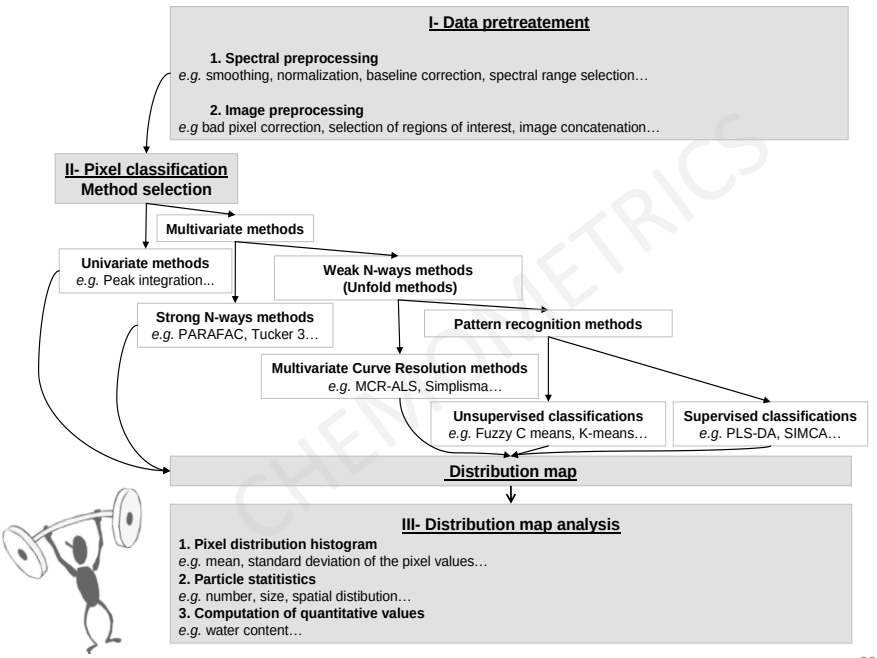

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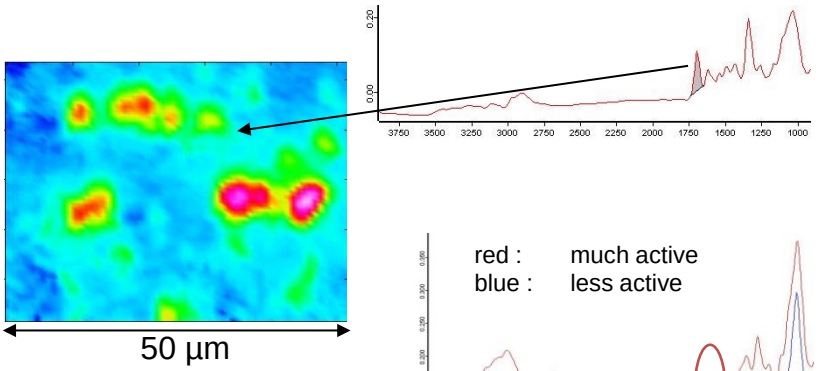
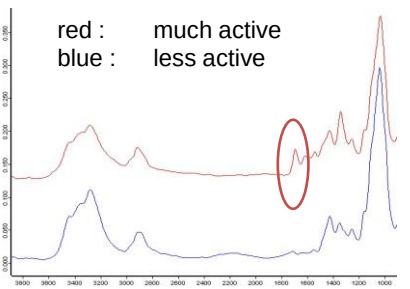
Surface image of a tablet



1720-1640 cm^{-1}
(IR peak of active)



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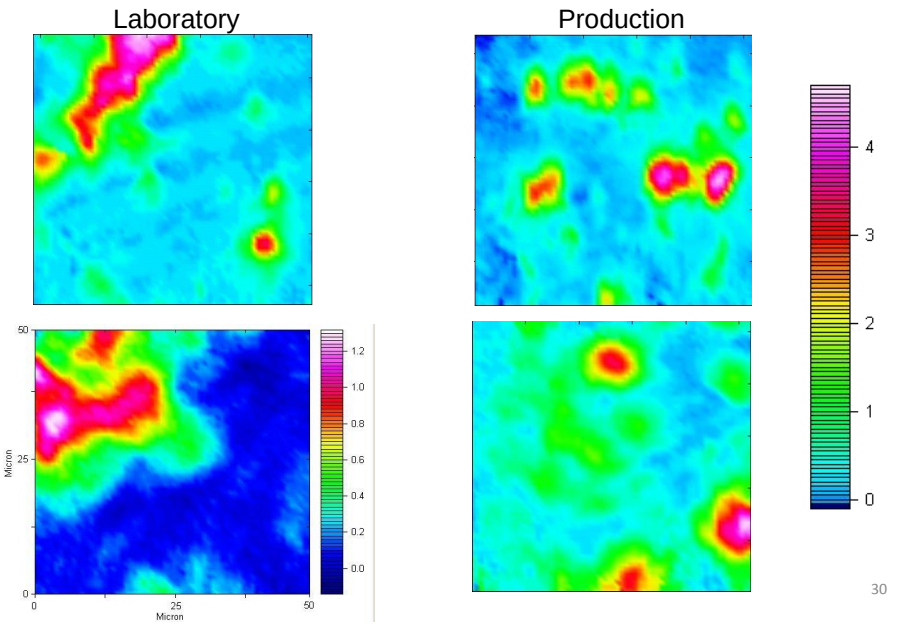
Laboratory vs. production **active ingredient, 1720-1640 cm^{-1}**



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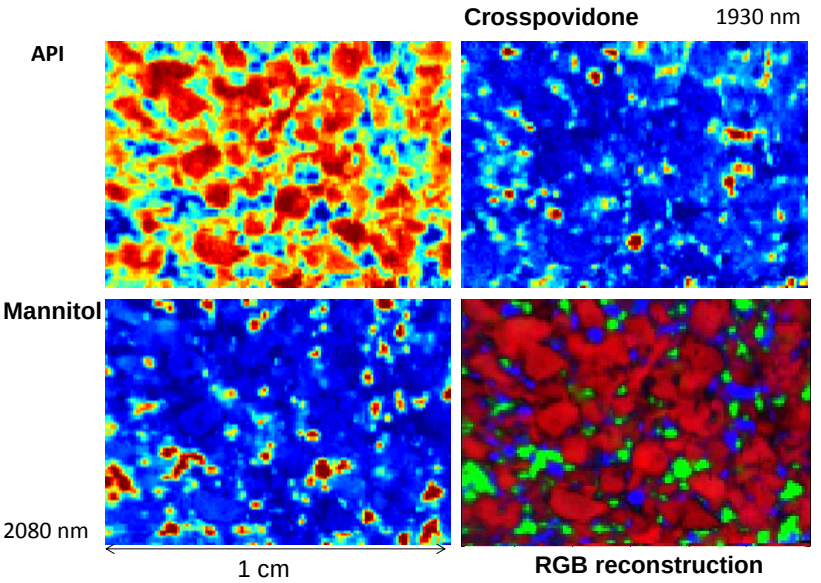
Distribution map of three components



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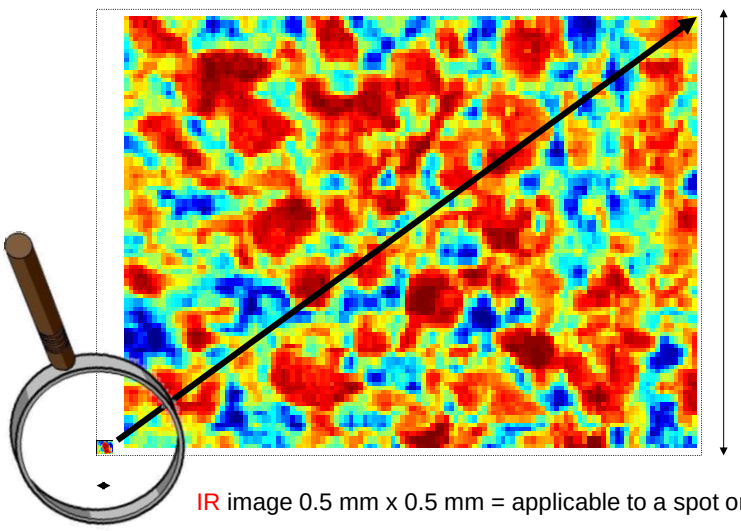
Scaling up regions of interest



NIR image
25 mm x 20 mm
= applicable to
the full tablet
surface
and even larger

IR image 0.5 mm x 0.5 mm = applicable to a spot on the surface

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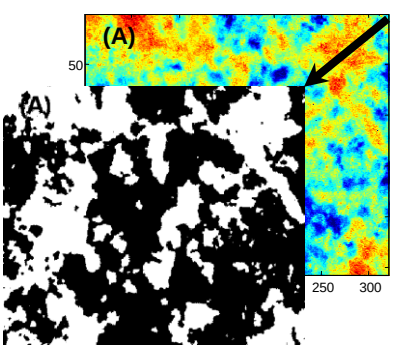
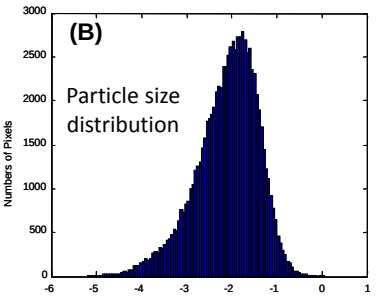
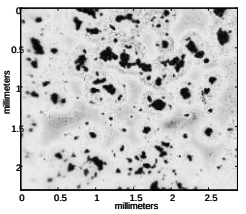
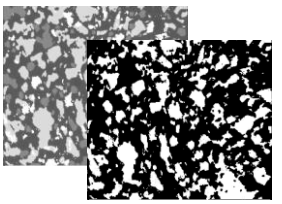
Analysing pixels





Focus on shape or dimensions



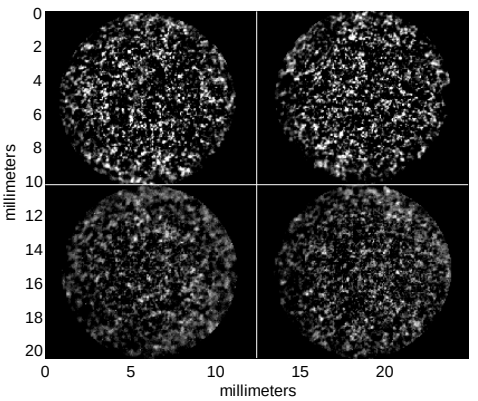


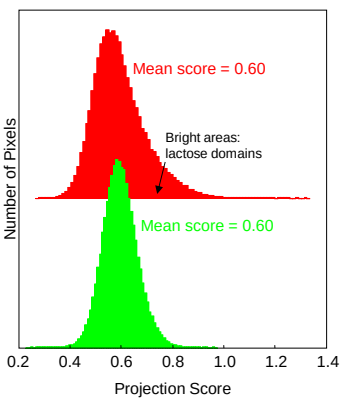
Adjusting contrast in black and white

33

Example: estimation of lactose abundance

Production site A vs B

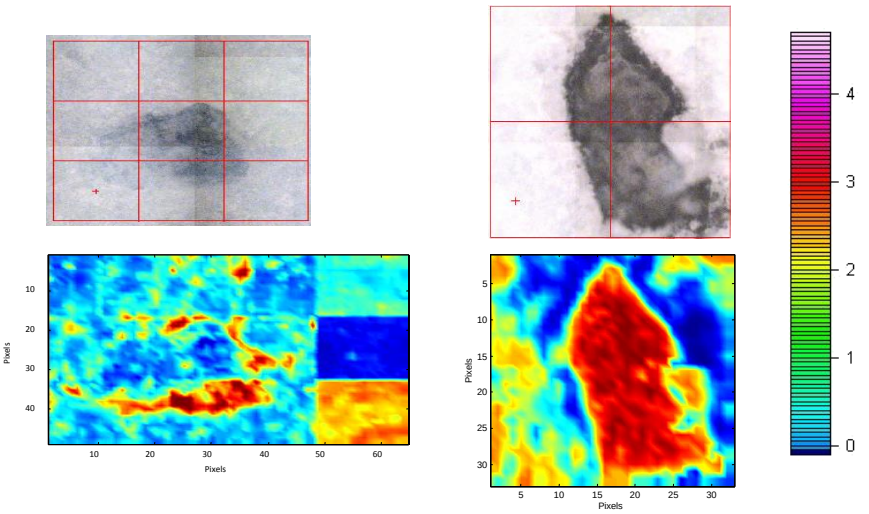




34

Analysis of a dark spot

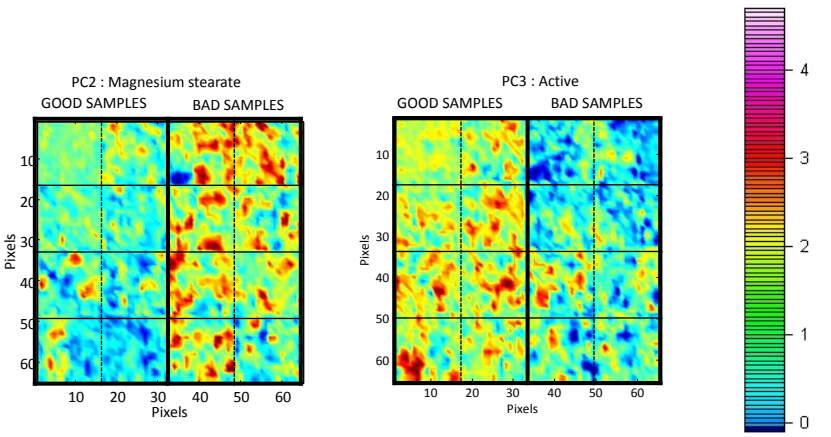
By imaging and PCA



35

Solving dissolution issue

Too much Mg stearate at the surface



36

Identification of counterfeits

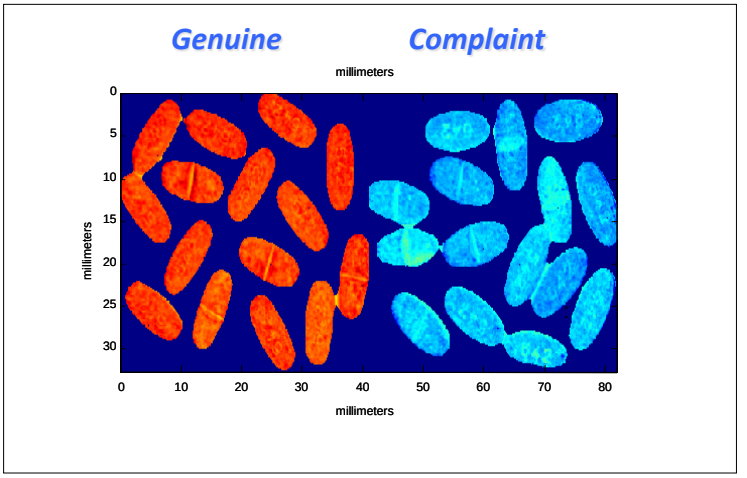


Image taken at a characteristic API wavelength
Size : 2 x (32.7 x 41 mm)

37

Chemical Imaging (5.24)

- Chapter provides concepts on hyperspectral imaging
- No stringent requirements
- Vibrational spectroscopy only was addressed
- Chemical imaging systems (CIS) are also platforms for (single point) spectroscopy
- Therefore, cross-linked to respective monographs
- And if CIS is used for single point spectroscopy, the respective monograph applies

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- Imaging technology is mature
- Meanwhile various instruments and set-ups are available
- Imaging comes on top of single spot spectroscopy with a high dosis of data collection, computation and smart algorithms
- Specific *chemometrics* and image analysis algorithms are required
- These are not addressed in this chapter

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Expected progress in…

- On-going improvements in handling, software, algorithms
- Miniaturization
- On-line sensing
- Three-dimensional *in-situ* imaging on track, however not covered by the chapter
- Combination of imaging sources i.e. multispectral approach

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Are new hyphenated technologies adequate for the European Pharmacopeia?

9th Edition Conference, 27-28 September, Tallinn, Estonia

Torbjörn Arvidsson, Prof.

Scientific expert at MPA, Adjunct professor Uppsala University, Vice Chair of the European Pharmacopeia Commission, Chair Group 10A

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Pharmaceutical Research and Development

- **Modern analytical techniques are commonly used in drug research in the pharmaceutical industries**
- **For characterisation of drug substances and drug products techniques such as NMR and LC-MS are more or less standard**
- **Can these techniques be used to a higher extent in quality control and in the pharmacopeia?**
  - 2.2.33. Nuclear magnetic resonance spectrometry
  - 2.2.43. Mass spectrometry

Nuclear magnetic resonance (NMR) spectroscopy

Possibilities with NMR

NMR spectra gives information about the chemical structure and the signals are quantitative

- **Identification**
- **Assay**
- **Water determination**
- **Residual solvent**
- **Related substances**
- **Replace HPLC amino acid analysis of peptides**
- **Viscosity and osmolality measurements**
- **Metal analysis using complexes**

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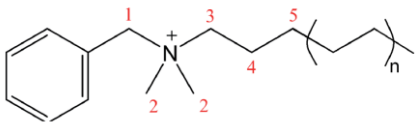
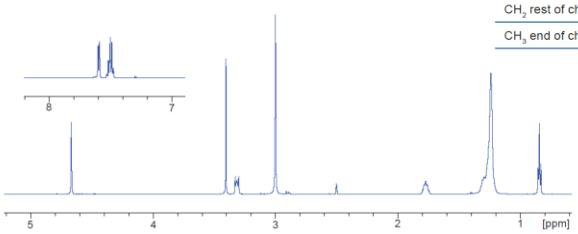
MEDICAL PRODUCTS AGENCY

Benzalkonium chloride, identification



	Chemical shift (ppm)	Number of protons
Benzyl	7.6, 7.5	5
1-CH_2	4.67	2
2-CH_3	3.00	6
3-CH_2	3.27	2
4-CH_2	1.78	2
5-CH_2	1.29	2
CH_2 rest of chain	1.24	mainly 16 or 20
CH_3 end of chain	1.84	3



Ref. I. McEwen, T. Arvidsson, Pharmeuropa Bio&SN October 2010 pp 87-102

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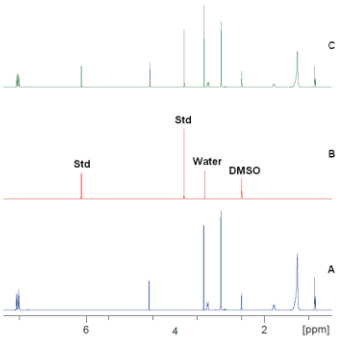
MEDICAL PRODUCTS AGENCY

Benzalkonium Chloride; Assay



Test sample and internal standard

Internal standard 3-sulfolene in DMSO

Benzalkonium chloride

$$Q(\%) = \frac{P(std) \cdot MW(subs) \cdot nH(std) \cdot m(std) \cdot A(subs)}{MW(std) \cdot nH(subs) \cdot A(std) \cdot m(subs)}$$

Equation 1

Quantification:

Where P = purity; MW = molecular weight; nH = number of protons; A = integral area; std = standard; subs = substance.

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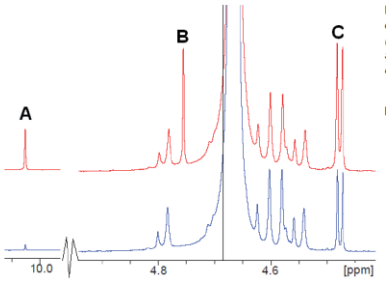
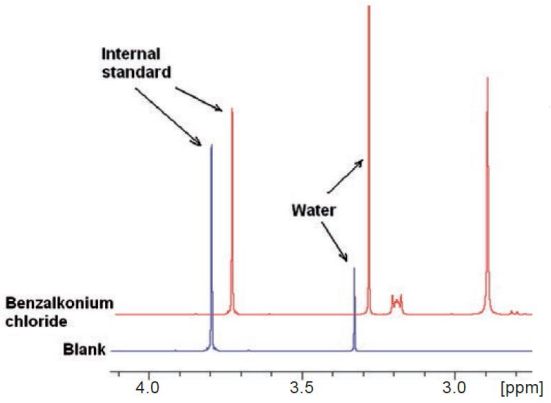
MEDICAL PRODUCTS AGENCY

Benzalkonium Chloride; Test of related substances



	Impurity	Found	Specified limit in monograph
C	Benzyl alcohol	0.14 % (RSD=7 %, n=3)	0.15 %
A	Benzaldehyde	0.01 % (RSD=30 %, n=3)	0.5 %
B	Benzyl chloride	Not present or less than 0.001 % (LOD)	0.05 %

Benzalkonium chloride, Water content



- 5.8 % water was found
- Manufacturer reported 6.0%

Advantages with quantitative NMR

- **Several different tests can be performed on one sample**
- **Quick - Answer in half a day**
- **General - No need for ”specific” internal standard**
- **Reliable - Comparable to GC, HPLC, titration**
- **Selective**

NMR in Ph.Eur

- **2.2.64 Peptide identification by nuclear magnetic resonance**

  Alternative test for identification in the monograph of Goserelin (1636) and Buserelin (1077)

- **5.16 Crystallinity**

  Describes various test to determine crystallinity e.g. Solid state NMR

- **Haemophilus type b and meningococcal group C conjugate vaccine (2622) and Haemophilus type b conjugate vaccine (1219)**

  In production section; characterization and identification of the linear copolymer polyribosylribitol phosphate

- **Meningococcal group C conjugate vaccine (2112) and Pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150)**

  In production session; Identification and serological specificity

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MEDICAL PRODUCTS AGENCY

NMR in Ph.Eur

- **Medronic acid for radiopharmaceutical preparations (2350)**

  Test of impurities

- **Tetra-O-acetyl-mannose triflate for radiochemical preparations (2294)**

  Test of impurity

- **Heparin calcium (0332), Heparin Sodium (0333), Heparin low-molecular-mass (0828)**

  Identification

- **Cod-liver oil (2398) and Salmon oil farmed (1910)**

  Identification and test of Positional distribution (β(2)-acyl) of fatty acids

- **Hydroxypropylbetadex (1804)**

  Assay

NMR in Ph.Eur

- **Lauromacrogol 400 (2046)**

  Average chain length of the fatty alcohol and average number of moles of ethylene oxide

- **Pemetrexed disodium heptahydrate (2637)**

  Identification, alternative method

- **Poloxamers (1463)**

  Oxypropylene:oxyethylene ratio

- **Starch hydroxypropyl (2165) and Starch hydroxypropyl pregelatinised (2645)**

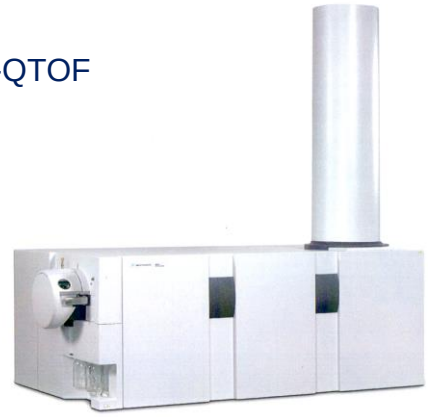
  Assay

- **Tobramycin (0645)**

  Assay

Liquid Chromatography–Mass Spectrometry (LC-MS)

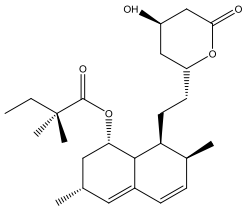
LC-MS-QTOF



Is it possible to trace the API manufacturer using chemical analysis?

Study outline:

- Fingerprinting of API using LC-MS/MS impurity profiling
- Separation and detection of Simvastatin related impurities using modern UPLC technology
- Highly selective and sensitive MS-QTOF detection
- Chemometric models to interpret data



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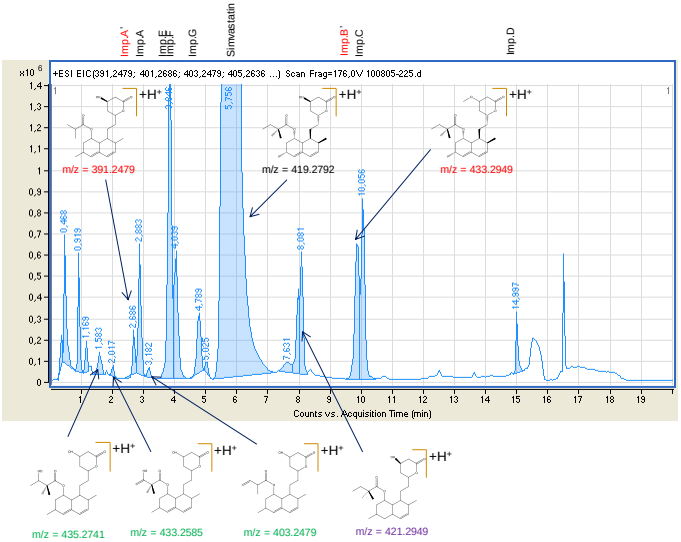
MEDICAL PRODUCTS AGENCY

UPLC optimisation



Selectivity – sensitivity - validation

- **LOQ simvastatin 8 ppm**
- **About 40 times lower as compared to UV detection**
- **Intraday precision at typical impurity level was about 4-6%**
- **Several new impurities (<< 0.1%) were identified**

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Study samples

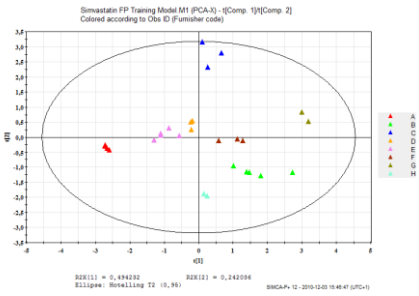
- 39 APIs originated from 9 different suppliers
- 21 Finished Products coming from 14 different manufacturers
- LC/MS impurity fingerprinting of 15 impurities related to Simvastatin.

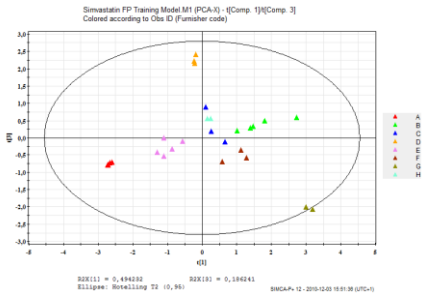
Data mining

6-variables PCA training model

Built on relative areas of 6 impurities:

m/z = 403.2479
Impurity E
Impurity F
Impurity G
Impurity B'
Impurity B





Explained cumulative Variation: 92.2%

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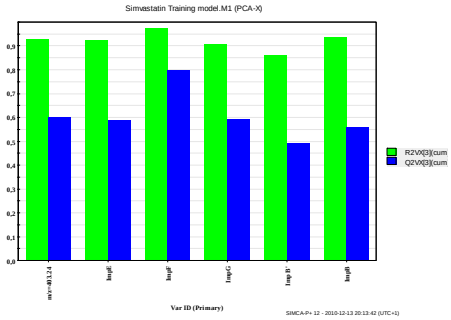
MEDICAL PRODUCTS AGENCY

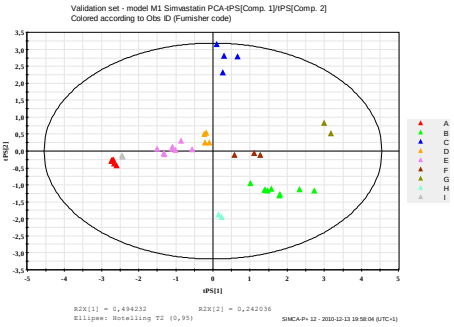
Validation

Cross validation



Very good explained variation R2 ≥ 0.9
Good predicted variation Q2 ≥ R2 – 0.3

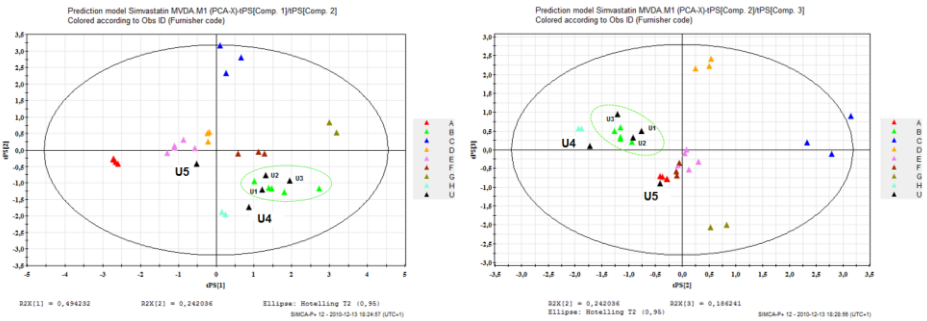
External Validation Test



All validation samples (16) fit to their respective groups

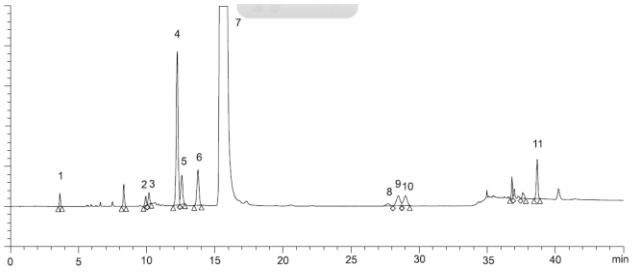
Application of the PCA model

Application to 5 unknown test samples



Samples U1, U2 and U3: Supplier B
Samples U4 and U5: unknown Supplier

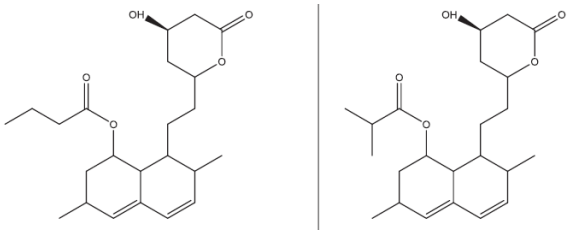
Simvastatin; Method for related substances published in Pharmeuropa 26.1



1. impurity H
2. impurity I
3. impurity A
4. impurity E
5. impurity F
6. impurity G
7. simvastatin
8. impurity B
9. impurity J
10. impurity C
11. impurity D

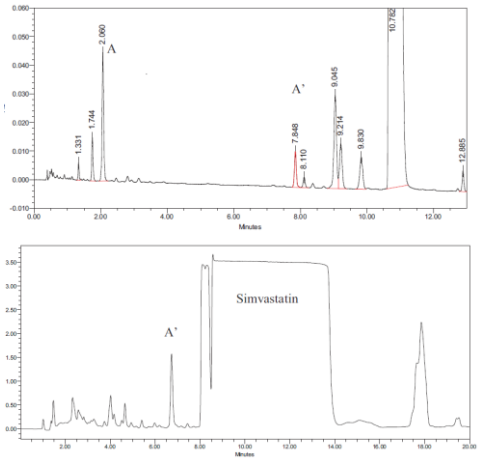
LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Impurity I (A´), Possible structure evaluated by LC-MS-TOF



LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Preparative chromatography of simvastatin impurity

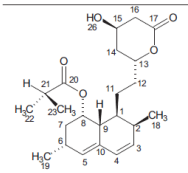


Simvastatin 15 mg/ml
Injection volume: 1 ml

45 preparative runs resulted in about 0.5 mg pure substance

NMR verification of the chemical structure

Table 2. Assignment of ^{1}H and ^{13}C NMR chemical shifts for Impurity A' in methanol-d_4 solution.

Structure	Atom	^{1}H chemical shift, ppm	^{13}C chemical shift, ppm
	1	1,73	38,1
	2	2,40	31,9
	3	5,79	134,1
	4	5,97	129,4
	5	5,51	130,2
	6	2,43	28,7
	7ab	1,97	33,3
	8	5,32	69,6
	9	2,34	38,3
	10	-	? (low S/N?)
	11a	1,49	24,6
	11b	1,39	24,6
	12a	1,83	33,8
	12b	1,40	33,8
	13?	4,64	77,7
	14a	1,93	36,3
	14b	1,74	36,3
	15?	4,25	63,2
	16a	2,71	39,1
	16b	2,53	39,1
	17?	-	180,2
	18	0,91	14,0
	19	1,07	23,1
	20	-	178,4
	21	2,51	35,6
	22 or 23	1,15	19,7
	22 or 23	1,12	18,8

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Mass spectrometry for identifcation in Ph. Eur.

- **Norflurane (2257)**
  - MS for identification and GC-MS for test of related substances

GC-MS methods in Ph.Eur.

- **2.5.37, Methyl ethyl and isopropyl methanesulfonate in methanesulfonic acid**
- **2.5.38, Methyl ethyl and isopropyl methanesulfonate in active substances**
- **2.5.39, Methanesulfonyl chloride in methanesulfonic acid**
- **2.5.40, Methyl ethyl and isopropyl toluenesulfonate in active substances**
- **2.5.41, Methyl ethyl and isopropyl benzenesulfonate in active substances**

LC-MS in Ph.Eur

- **2.2.59 Glycan analysis of glycoproteins**

  General chapter; LC or CE coupled with MS is recommended for analysis of intact glycoprotein, glycopeptides and glycans
- **Interferon beta-1a concentrated solution (1639)**

  Production session: Identification using MS or LC-MS
- **Meldonium dihydrate (2624)**

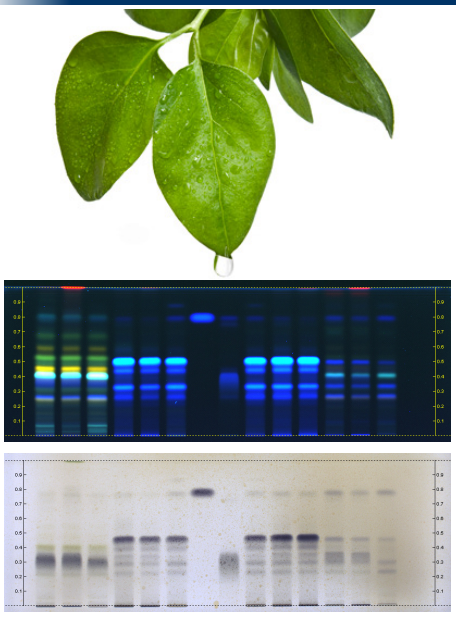
  Test of related substances
- **Oseltamivir phosphate (2422)**

  Test of Impurity B
- **Imatinib mesilate (2736)**

  Test of Impurity F

Concluding remarks

- **Mass spectrometry coupled to GC or LC are rarely used in Ph. Eur.**
- **NMR is more used than MS and methods for identification or quantitative determination are included in 17 monographs**
- **Are new hyphenated technologies adequate for Ph. Eur?**
  - Yes! From a scientific point of view an increased involvement of these techniques in Ph. Eur. would is of great value



HPTLC for herbal drugs and herbal drug preparations

Prof. Dr. Salvador Cañigueral

Unit of Pharmacology, Pharmacognosy, and Therapeutics
Faculty of Pharmacy and Food Sciences
Barcelona, Spain

HPTLC for herbal drugs and herbal drug preparations

Content

1. Herbal medicinal products (HMP)
2. HPTLC *versus* TLC
3. TLC/HPTLC in quality control of herbal products
4. The issues
5. The improvements: Chapter *2.8.25* of the *Ph. Eur.*
6. Future developments

Herbal medicinal products

Active substance + **Dosage form**

Herbal preparations

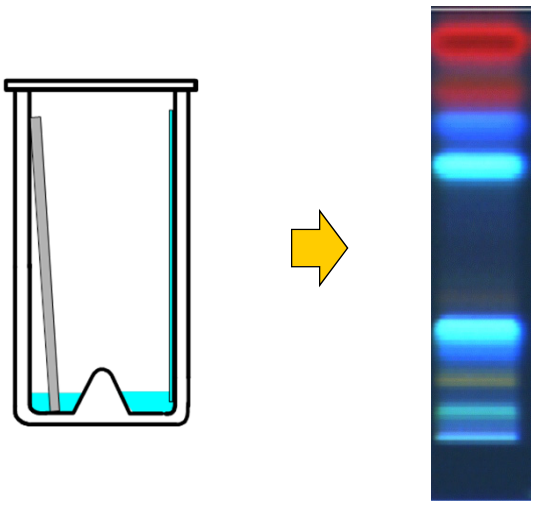
- ✓Herbal drugs
- ✓Extracts
- ✓Essential oils
- ✓Etc...

Complexity !

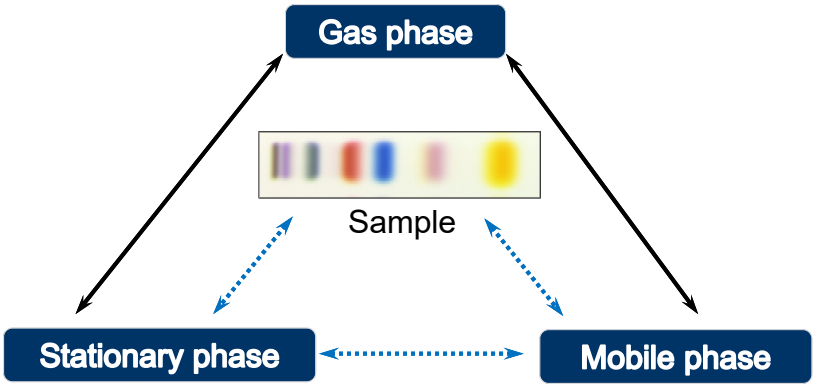
- ✓Tablets, pills
- ✓Capsules
- ✓Drops, syrups
- ✓Creams, ointments
- ✓Suppositories
- ✓Tee preparations
- ✓Soluble tee preparations

Etc.

Thin layer chromatography (TLC)



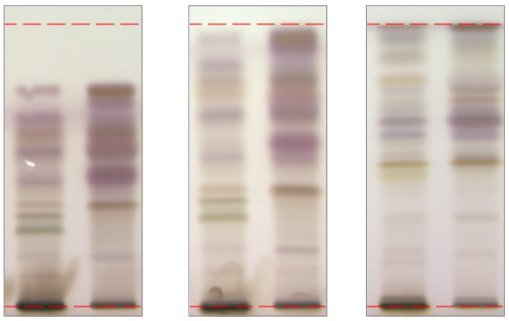
The planar chromatographic system



The gas phase

Chamber conditioning

Preconditioned Saturated Unsaturated



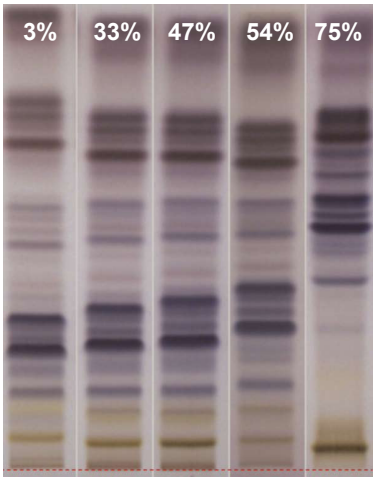
HPTLC silica gel 60 F_{254},toluene: ethyl acetate: acetic acid (70: 33: 3)

Left:*S. chinensis*, right:*S. sphenanthera*

Thin layer chromatography

Humidity / Activity

HR: 3% 33% 47% 54% 75%



Affects:

- Values of R_F:
  ↑ Activity → ↓ R_F
- Separation

➡ **Should be controlled!**

Chromatographic profile of *Hoodia gordonii a*t different humidity (HR).

The TLC steps

Sample preparation

↓

Application

↓

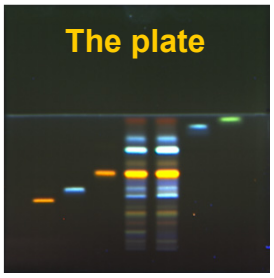
Development

↓

Detection / quantitative evaluation

↓

Documentation

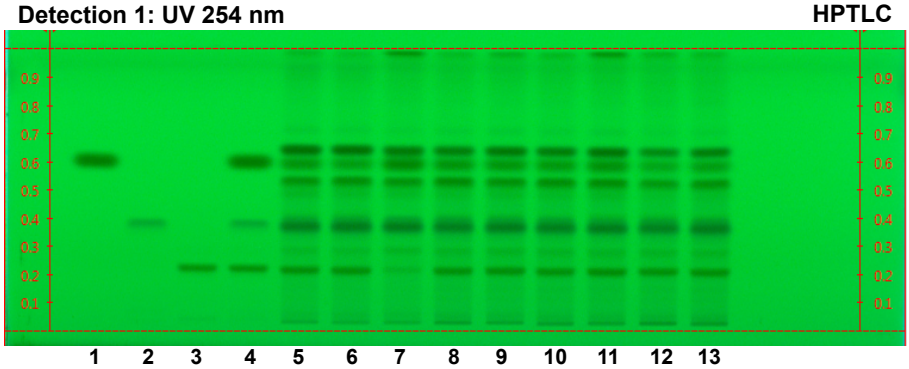


Flexibility

Multiple detection

Mate leaf (*Ilex paraguariensis*)

Detection 1: UV 254 nm **HPTLC**

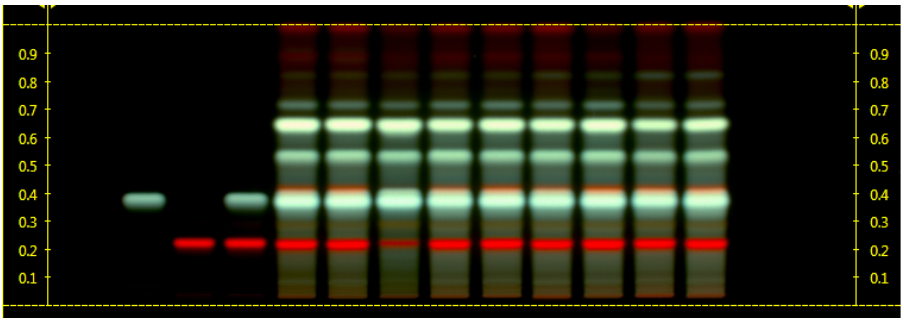


1. Caffeine
2. Chlorogenic acid
3. Rutin
5-13. Mate leaf samples

Multiple detection

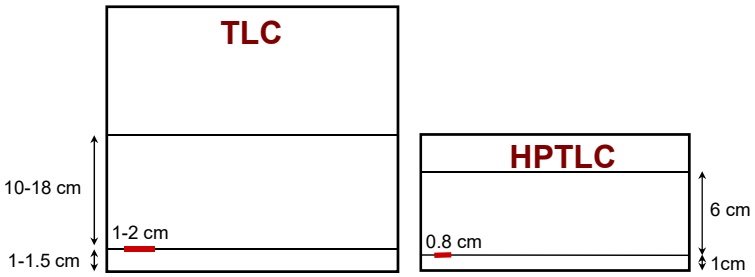
Mate leaf (*Ilex paraguariensis*)

Detección 2: NPR + PEG / UV 365 nm **HPTLC**



1. Caffeine
2. Chlorogenic acid
3. Rutin
5-13. Mate leaf samples

TLC *versus* HPTLC

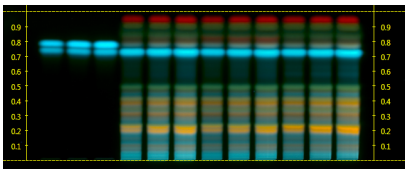


✓ Average particle size:	10 -15 µm	5 -7 µm
✓ Particle size distribution:	Wide	Narrow
✓ Layer thickness	250 µm	100-200 µm
✓ Application volume:	10-20 (-50) µL	1-5 µL
✓ Nº samples/plate:	max. 12	> 12
✓ Development duration:	30-200 min	3-20 min
✓ Solvent consumption:	50 ml	5-10 ml
✓ Detection limit: Absorbance:	100-1000 ng	10-100 ng
Fluorescence:	1-100 ng	0.1 to 10 ng

Quality of herbal drugs and herbal preparations

Objectives

HPTLC



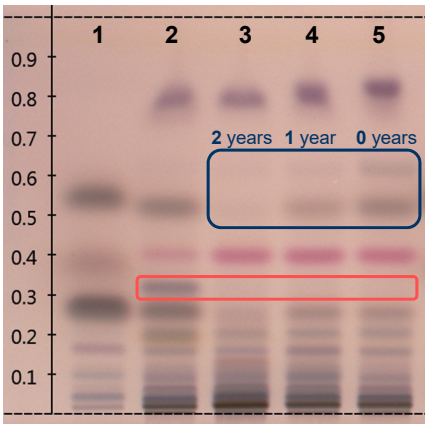
Stability

Quality control

- Identity
- Purity
  Contaminants
- Quantitative determination of active principles and markers

Identification / purity / stability

Lavender flower (*Lavandula angustifolia*)



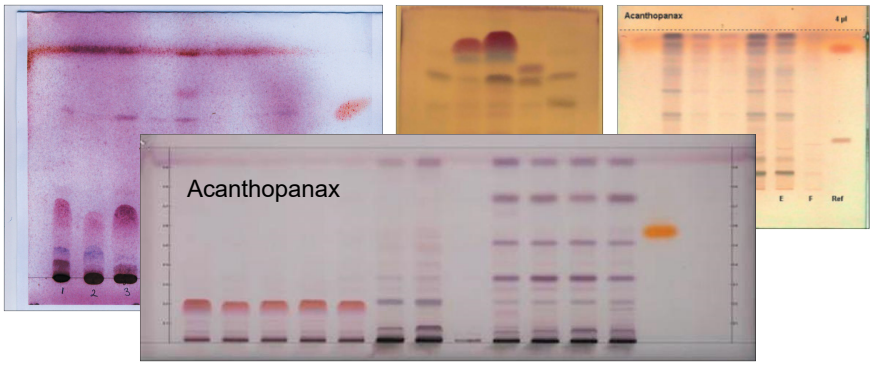
Detection: anisaldehyde reagent, 100-105 °C (5-10 min) / daylight

HPTLC
1. Reference solution
2. Lavandin flower
3. Lavender flower (2010, t = 2 years)
4. Lavender flower (2011, t = 1 year)
5. Lavender flower (2012, t = 0 years)

Identification by TLC

Problems

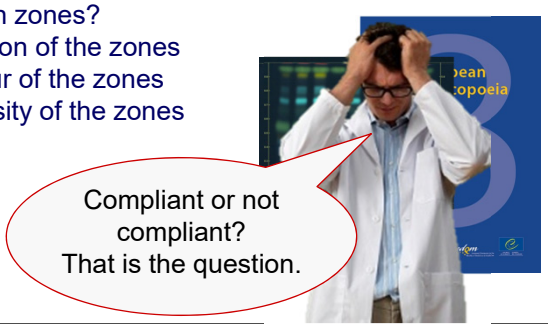
- ✓ **Variability of the chromatograms**
  - Variability of herbal drugs (differences between batches)
  - Lack of reproducibility intra- and inter-laboratory



Identification by TLC

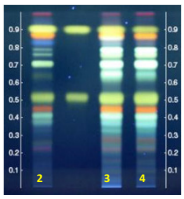
Problems

- ✓ **Interpretation of the chromatograms**
  - Difficulties for describing the natural variability in a single description
  - Is the chromatogram well done?
  - Difficulties for describing and interpreting:
    - Which zones?
    - Position of the zones
    - Colour of the zones
    - Intensity of the zones

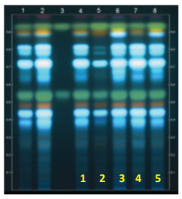


HPTLC *versus* TLC

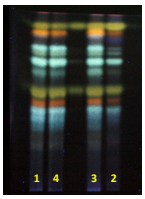
TLC reproducibility



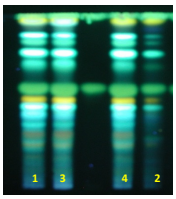
Laboratory 1
(glass plate F_{254})



Laboratory 2



Laboratory 3

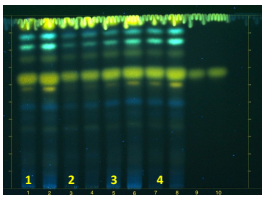


Laboratory 4

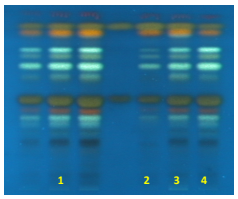
Roman chamomile flower

TLC

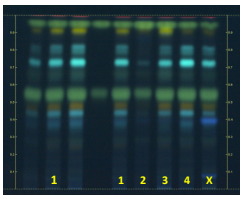
Ph. Eur. Inter-laboratory trial



Laboratory 5
(the *1.5-fold* application vol is additionally applied)



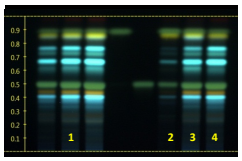
Laboratory 6



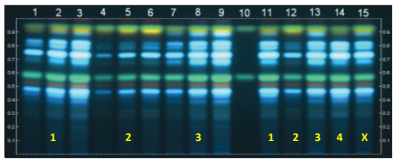
Laboratory 7

HPTLC *versus* TLC

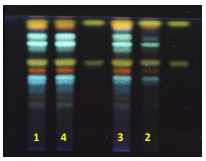
HPTLC reproducibility



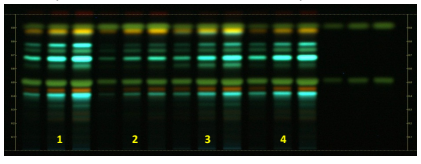
Laboratory 8



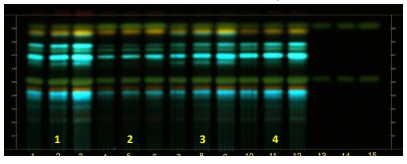
Laboratory 2



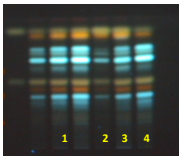
Laboratory 3



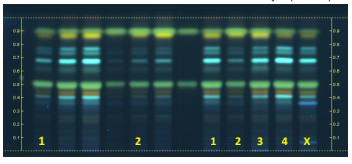
Laboratory 5 (instrumental)



Laboratory 5 (manual)



Labortory 6



Laboratory 7

Roman chamomile flower

HPTLC

Ph. Eur. Interlaboratory trial

HPTLC for identification of herbals

Ph. Eur. Improvements (*chapter 2.8.25*)

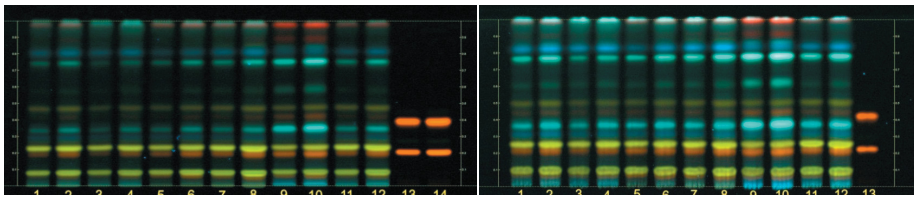
1. Improvement of reproducibility

- ✓ **Introduction of HPTLC**
  Instrumentation may help

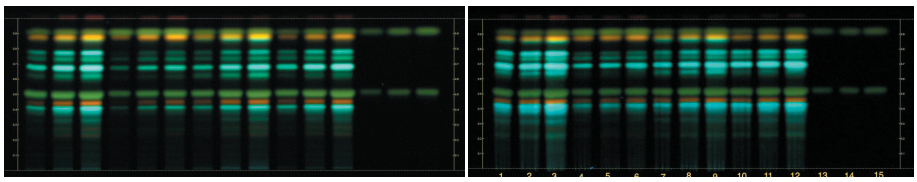
Ph. Eur. collaborative trial

Instrumental *versus* manual HPTLC

Instrumental HPTLC **Manual HPTLC**



Calendula



… Roman Chamomile; Crataegus; Hypericum, Birch …

HPTLC for identification of herbals

Ph. Eur. improvements (*chapter 2.8.25*)

1. Improvement of reproducibility

- ✓ Introduction of HPTLC
- ✓ **Standardisation of methodology**

Standard operating protocols (SOP)

Reproducibility ⇦ Standardization of methodology ⇦ SOP

- ✓ Sample preparation
- ✓ Plate setup and handling
- ✓ Sample application (as band)
- ✓ Chamber geometry and saturation
- ✓ Humidity control
- ✓ Developing distance
- ✓ Derivatisation procedure
- ✓ Documentation (electronic images)
- ✓ Evaluation

} **SOP**

Reich, E., Schibli, A. (2004). J. Planar Chromatogr. 17, 438-443

HPTLC for identification of herbals

***Ph. Eur.* improvements** (*chapter 2.8.25*)

1. Improvement of reproducibility

- ✓ Introduction of HPTLC
- ✓ Standardisation of methodology
- ✓ **Introduction of a system suitability test** (qualification of the plate)

System suitability test (SST)

Ph. Eur. 2.8.25

SST

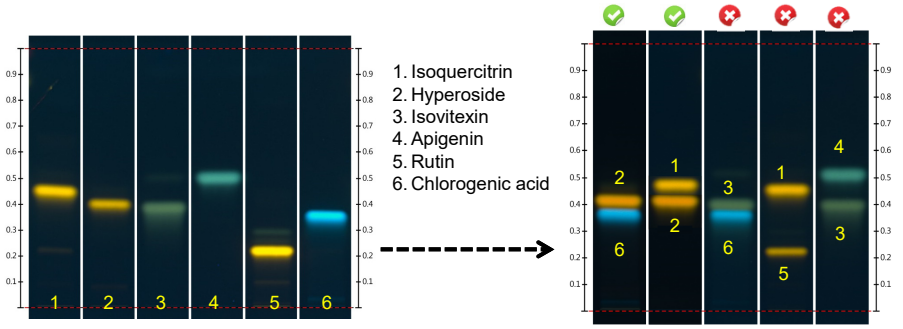
Test is based on the **separation of 2 substances** that have **similar retardation factor**s (R_F values) **but** that are barely **separable** under the specified chromatographic conditions.

System-specific suitability test (SST)

Ph. Eur. 2.8.25

Flavonoids

Developing solvent: Ethyl acetate / formic acid / water (80:10:10)



HPTLC for identification of herbals

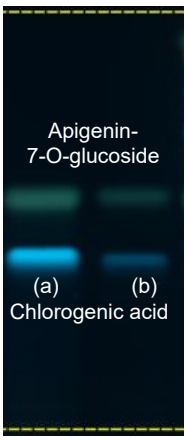
***Ph. Eur.* improvements** (*chapter 2.8.25*)

2. Improvement of the description and interpretation of the chromatograms

- ✓ **Sequence and characteristics of the zones**
  - Number
  - Position
  - Colour: encompassing description of zone colours
  - **Intensity: introduction of an intensity marker**

Introduction of an intensity marker

Ph. Eur. 2.8.25



R R¼

4-fold dilution

Example of intensity marker: chlorogenic acid (CA)

Visual intensity description

Intense zone:
More intense than CA zone intensity (a)

Zone with no descriptor for intensity:
Similar in intensity to CA zone intensity (a)

Faint zone:
Less intense than CA zone intensity (a) but equal to or more intense than CA zone intensity (b)

Very faint zone:
Less intense than CA zone intensity (b)

R and R¼: Reference solutions

HPTLC for identification of herbals

Ph. Eur. improvements (*chapter 2.8.25*)

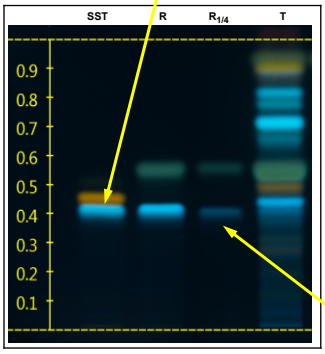
Roman chamomile flower

System-specific suitability test (SST)

Description table

Upper edge of plate	
	A greenish-blue fl zone (apigenin) A weak to equivalent brownish-yellow or orange fl zone
	Three light blue fl zones (upper two with a weak to equivalent intensity, the lowest usually intense)
Apigenin-7-glucoside : A greenish-blue fl zone	A equivalent to intense greenish-blue fl zone (apigenin-7-glucoside) A weak to equivalent brownish-yellow or orange fl zone
Chlorogenic acid: A light blue fl zone	A weak to equivalent light blue fl zone
Reference solution	**Test solution**

_____: Marks between upper, middle and lower third



Typical chromatogram

Intensity marker

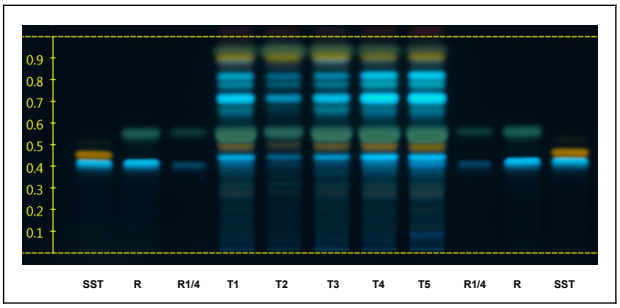
SST: Reference solution (c)
R: Reference solution (a)
$R_{¼}$: Reference solution (b). R diluted with factor 4
T: Test solution (T1)

HPTLC for identification of herbals

Ph. Eur. improvements (*chapter 2.8.25*)

Example chromatograms of different batches

Roman chamomile flower



SST: Reference solution (c),
R: Reference solution (a),
$R_{1/4}$: Reference solution (b): R diluted with factor 4

T1-T5: Test solutions Chamomillae romanae flos
HPTLC-plate has been dipped for derivatization

HPTLC for identification of herbals

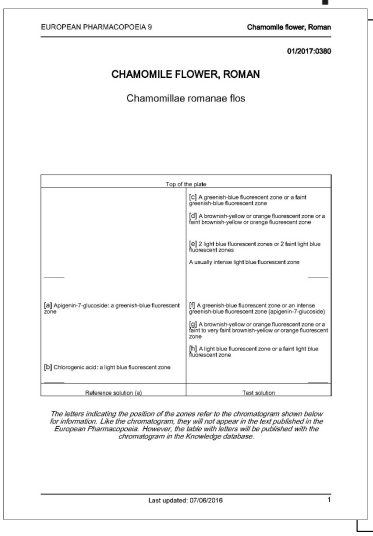
Ph. Eur. improvements (*chapter 2.8.25*)

2. Improvement of the description and interpretation of the chromatograms

- ✓ Sequence and characteristics of the zones
- ✓ **Publication of colour pictures of chromatograms**
  - Not in the Pharmacopeia itself but in the Knowledge database (available online for subscribers).
  - Not mandatory, given only as information.
  - Including several batches to show natural variability.

HPTLC for identification of herbals

Ph. Eur. improvements (*chapter 2.8.25*)



EUROPEAN PHARMACOPOEIA 9 — Chamomile flower, Roman

01/2017:0380

CHAMOMILE FLOWER, ROMAN

Chamomillae romanae flos

Top of the plate

[a] Apigenin-7-glucoside: a greenish-blue fluorescent zone

[b] Chlorogenic acid: a light blue fluorescent zone

[c] A greenish-blue fluorescent zone or a faint greenish-blue fluorescent zone

[d] A brownish-yellow or orange fluorescent zone or a faint brownish-yellow or orange fluorescent zone

[e] 2 light blue fluorescent zones or 2 faint light blue fluorescent zones

A usually intense light blue fluorescent zone

[f] A greenish-blue fluorescent zone or an intense greenish-blue fluorescent zone (apigenin-7-glucoside)

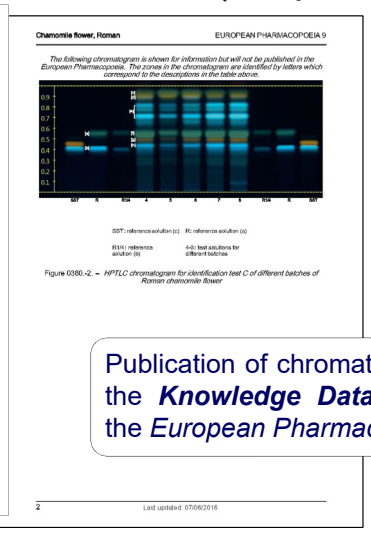
[g] A brownish-yellow or orange fluorescent zone or a faint to very faint brownish-yellow or orange fluorescent zone

[h] A light blue fluorescent zone or a faint light blue fluorescent zone

Reference solution (a) | Test solution

The letters indicating the position of the zones refer to the chromatogram shown below for information. Like the chromatogram, they will not appear in the text published in the European Pharmacopoeia. However, the letter with letters will be published with the chromatogram in the Knowledge database.

Last updated: 07/06/2016 — 1



Chamomile flower, Roman — EUROPEAN PHARMACOPOEIA 9

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia. The zones in the chromatogram are identified by letters which correspond to the descriptions in the table above.

SST: reference solution (c) R: reference solution (a)

R1/4: reference solution (b) 4–6: test solutions for different batches

Figure 0380.-2. – *HPTLC chromatogram for identification test C of different batches of Roman chamomile flower*

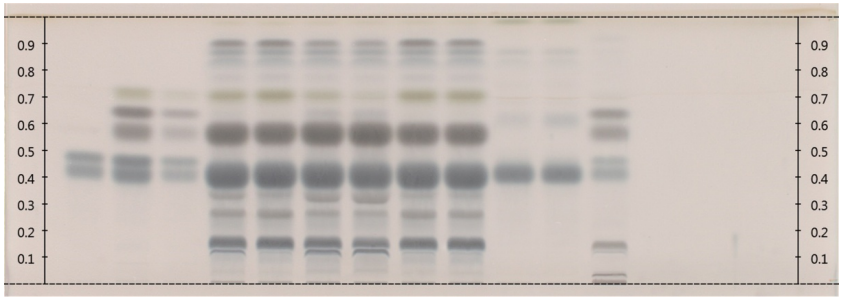
2 — Last updated: 07/06/2016

Publication of chromatograms in the ***Knowledge Data Base*** of the *European Pharmacopoeia*

HPTLC for identification of herbals

Polysaccharide containing drugs

According to the new *Ph. Eur.* rules and style



1: Acacia, roller-dried
2,3,6: Acacia
4,5: Acacia, spry-dried

7,8: Agar
9: Tragacanth

Quality control of herbal products

Which compound(s) should be assayed?

Frequently, the active principles are totally or partially unknown

A	B	C
The compounds responsible of the therapeutic activity are known	The active compounds are partially known	The active compounds are unknown
Constituents with known therapeutic activity	**Active markers**	**Analytical markers**

Quality control of herbal products

Are analytical markers relevant?

Herbal medicinal products

"… the herbal drug or herbal drug preparation in its **entirety** is regarded as the active substance..."

- ✓ Quantification **can help** in the control of the **manufacturing process**
- ✓ In many cases, the content of analytical marker(s) is **not indicative of the suitability of the herbal drug for the intended use**
- ✓ **Does not guarantee the quality nor the stability** of the herbal drug.

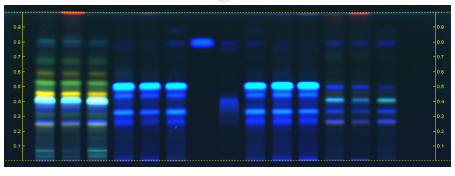
Quality control of herbal products

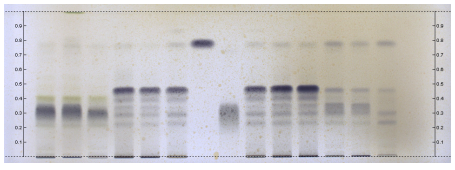
Is any better alternative to the assay of analytical markers?

- ✓ A **more holistic approach** would be suitable.
- ✓ The approach would be able to evaluate the **strength** of the herbal drug / preparation / product.

To be considered: more in deep exploitation of HPTLC profiling.

Under discussion! Research and concept definitions are needed!





Thank you very much for your attention

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Barcelona, Spain
UNIVERSITAT DE BARCELONA

Global Technical
Research & Development
QA

Quality Aspects in Continuous Manufacturing

Dr. Eric J.M. Meier
Novartis Pharma AG
QA Lead for Continuous Manufacturing

EDQM International Conference
27. / 28. September 2016

NOVARTIS

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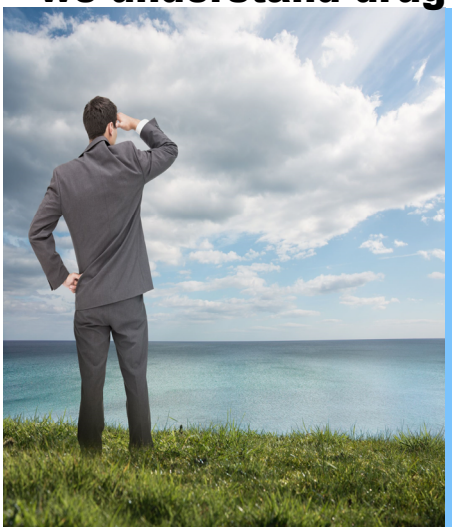
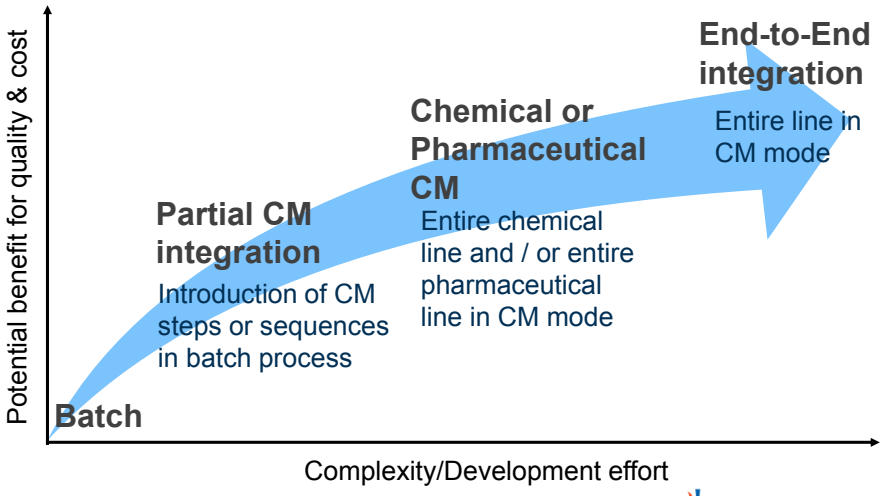
CM could dramatically change the way we understand drug manufacturing.

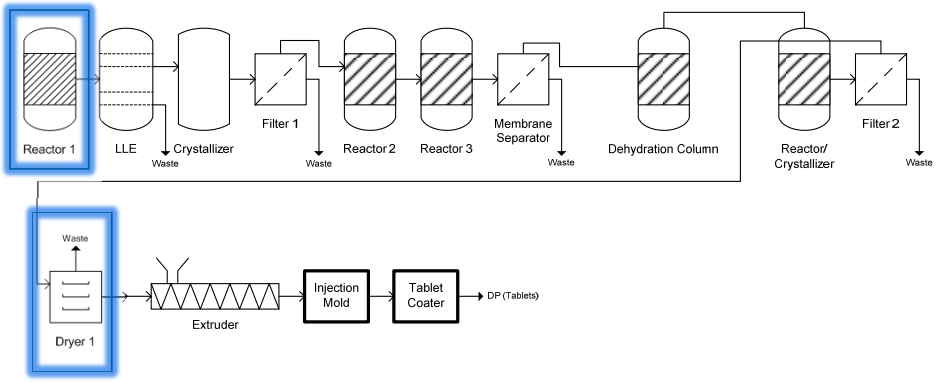


A unique opportunity to **redefine** the **industry paradigm** of how drugs are produced & pave the way to an even **faster**, **more precise** & **reliable** manufacturing approach.

Implementation Scenarios from Batch to CM

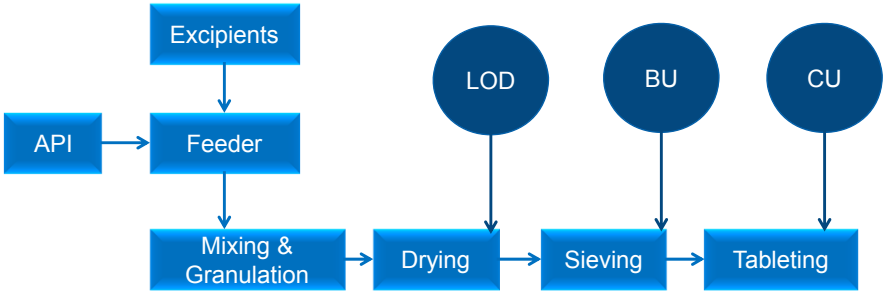


End-to-End Approach



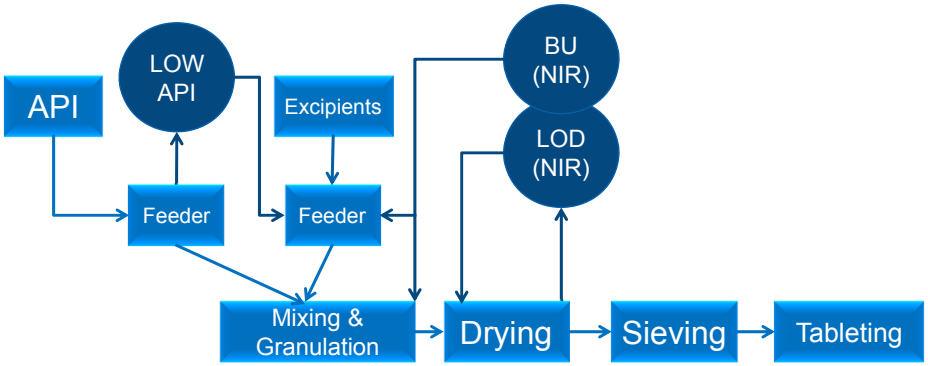
Continuous manufacturing train: the sum of multiple unit operations.

Control Strategy and Off-Line IPC



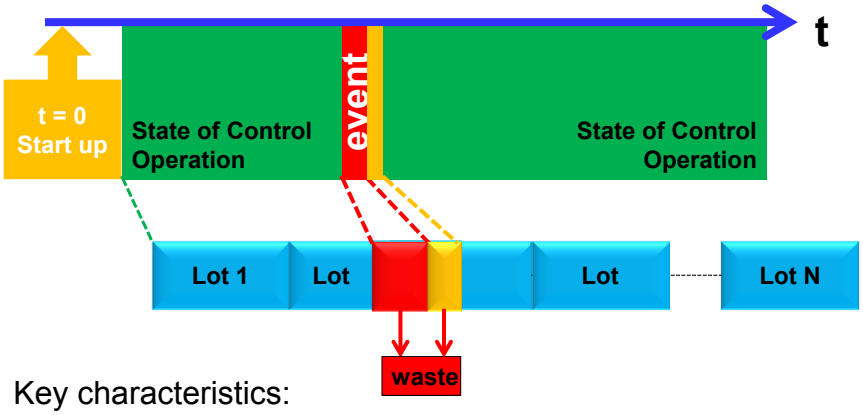
- Traditional IPC samples to monitor process
- Support of PAT development
- Confirmation and back up of PAT methods

Control Strategy and PAT



- Multiple physical principles assess state of process
- Primary objective: verification of robust operation, but: allow feedback and feedforward loops, if required

State of Control Operation



Key characteristics:

- Material collection in state of control operation
- Events are basis for flagging and diversion decision
- Divert material at the appropriate point of the CM process

Compendial standards & guidelines relevant to CM control strategy

- Pharmaceuticals produced by CM need to comply with current applicable Ph.Eur. monograph and GMP standards.
- Examples were Ph.Eur. likely is relevant and applicable:
  - Near-infrared spectroscopy (2.2.40);
  - Raman spectroscopy (2.2.48);
  - Demonstration of uniformity of dosage units using large sample sizes (2.9.47); etc.
- Other examples of areas covered by compendial monograph: physical and physicochemical methods e.g. monographs on spectroscopy, monographs on chromatography, etc.

Other standards & guidelines relevant to CM

- **ICH guidelines** e.g. ICH Q8, Q9, Q10, Q11
- **EU guidelines** e.g. EU guideline for Good Manufacturing Practice,
  Annex 15: Qualification and Validation;
  Annex 17: Real Time Release Testing;
- **Standards and white papers** e.g.
  - ASTM International Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry, E2968-14, 2015;
  - Regulatory and Quality Considerations for Continuous Manufacturing. May 20–21, 2014 Continuous Manufacturing Symposium, published by Allison et al, Journal of Pharmaceutical Sciences, 104: 803-812, 2015.

Conclusion on regulatory situation in continuous manufacturing

- Current regulatory framework is adequate to apply continuous manufacturing.
- Current regulations and guidelines are supportive for the development and manufacture of pharmaceutical continuous manufacturing processes.

Do Regulations Inhibit Implementation of CM?

Feedback from a survey of Efpia (European federation of pharmaceutical industries and associations)

efpia

- Current Regulatory Framework Does Not Prevent Implementation of Continuous Manufacturing
  - A number of EFPIA member companies have successfully registered continuous manufacturing processes.
  - Continuous manufacturing can be defined in a number of ways depending on process technology.
  - Continuous manufacturing implementation approaches can be diverse within and between companies.

Do Regulations Inhibit Implementation of CM?

Feedback from a survey of Efpia

- However industry addresses possible areas for clarification (e.g. through Q&A?):
  - **Batch Definition**
  - Definitions for Harmonized Terminology
  - Adaptation of CTD Structure
  - **Electronic data handling** for large data volumes in CM environment
  - **Batch Release Requirements**
  - **Process Validation**
  - Etc.

What is a batch, lot etc.? EU Definition.

Glossary of the EU GMP Guideline:

A batch is a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.
Note: In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

What is a batch, lot etc.? EU Definition.

EU GMP Guide, Part II (ICH Q7), Glossary:

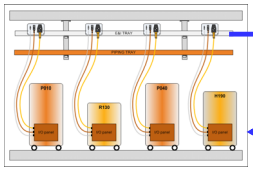
A batch is a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

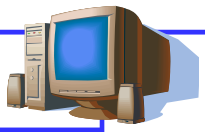
Batch Size

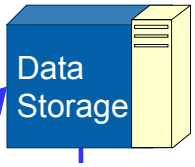
In traditional discrete manufacturing, the lot size is a technical consequence, e.g. limited by the amount of the same initial incoming mass.

In the continuous manufacturing mode batch and lot sizes are decoupled from such constraints.
The batch size (and run times) can now be based on the size of each order, balancing acceptable business risk and effectiveness.

Continuous Monitoring
Automation and Big Data







Process Control System

Data evaluation

Data collection
- CPP
- Parameters that influence process performance
- CQA
- PAT
- Events
- Room monitoring
- Etc.

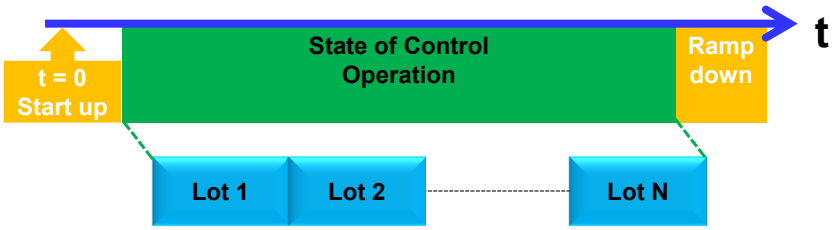
State of Control Operation

Release

Global TRD Quality

NOVARTIS

Batch Release



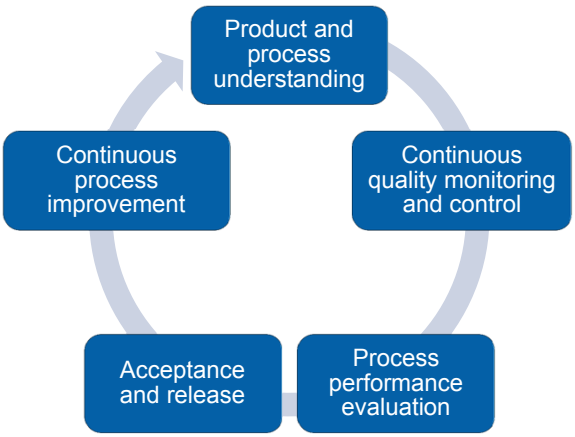
- Material collection in state of control operation
- Material from events or deviations diverted / segregated
- Deviations investigated and closed
- Batch records reviewed
- Process data, IPC, PAT, room & media data meet requirements
- Missing final product attributes characterized or RTRT (real time release testing) done

Global TRD Quality

NOVARTIS

Validation Approach: Continuous Verification

Continuous verification occurs over the lifecycle of a product:



[ASTM E2537]

Based on the large amount of data generated until and including **process performance qualification** (PPQ), no classical validation batches will be manufactured.
The **continuous performance verification** shall be used as an alternative validation approach.

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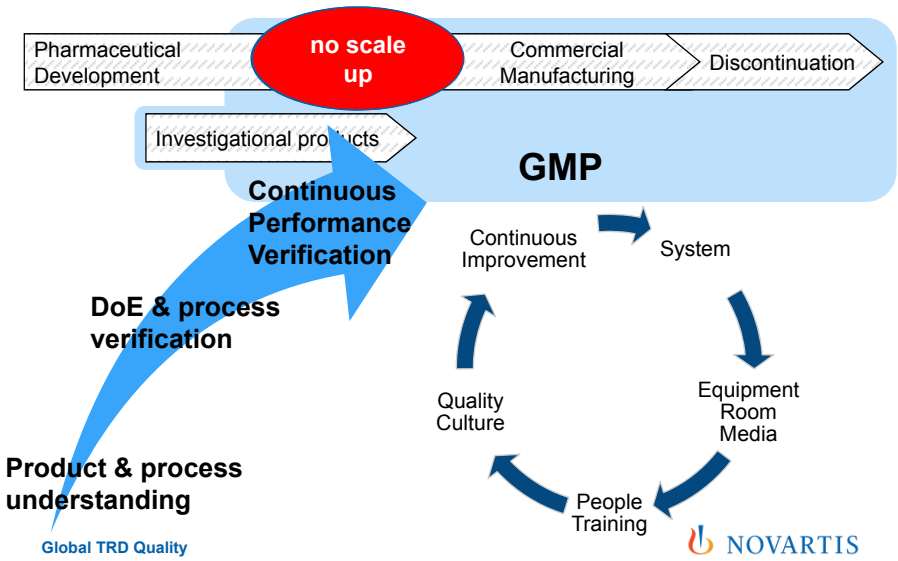
Lifecycle Approach: DoE – CpV – Routine



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Conclusion

- The current regulatory framework is supportive for the development, manufacture and application of pharmaceutical continuous manufacturing.
  - Ph.Eur. is supportive for the development and manufacture of pharmaceutical continuous manufacturing processes.
- Certain aspects of CM may benefit from regulatory clarification to fully realise all benefits from continuous manufacturing technology e.g. continuous performance verification or RTRT.
- CM is a topic of considerable interest and further discussion between industry, compendial authorities and regulatory agencies will be beneficial to ensure an appropriate regulatory framework that encourages innovation while protecting public health.

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- TechOps
- Reg-CMC
- Quality