

**QUALITY ON THE MOVE
DYNAMICS OF THE EUROPEAN PHARMACOPOEIA**

**Workshop Session
Pharmaceutical Dosage Forms & ST**

Moderators: H. G. Kristensen & C. Graffner

14:00-15:30

Dosage form monographs and standard terms. How the system is constructed and works, and future developments.

Budapest 2004-10-05
Christina Graffner

Signed Convention on the Elaboration of Ph.Eur.

Official standards published in Ph.Eur. are the legal and scientific basis for quality control of medicines.

Annex I Directive 2003/63/EC

Mandatory character of general monographs, specific monographs and monographs on dosage forms in the Ph. Eur. for marketing authorisation dossiers on medicines for human use.

**NOTICE TO APPLICANTS: CTD-
Guideline, Module 3 (Quality):**

“Wherever relevant, the requirements of Ph.Eur. apply: specific monographs, general monographs and general chapters.”

Demonstrating compliance with the Ph. Eur. standards is a necessary part of the marketing authorisation dossier for a medicine.

The Ph. Eur. standards is also used by e.g. health authorities to check the quality of marketed medicines.

New chapters and monographs of Ph.Eur.

- Identification of need
- Development of draft in expert group by instructions from European pharmacopoeia commission
- Consultation phase via Pharmeuropa
- Finalisation in expert group
- Adoption in European Pharmacopoeia Commission



Texts in Ph.Eur. controlling quality standards for dosage forms

- GENERAL CHAPTERS
 1. General
 2. Methods of analysis
 - 2.9 Pharmaceutical technical procedures
 3. Materials for containers, and containers
- GENERAL MONOGRAPHS
- MONOGRAPHS OF DOSAGE FORMS

GENERAL NOTICES apply to all monographs and other texts of Ph.Eur

- A preparation must comply throughout its period of validity
- Statements in monographs constitute mandatory requirements
- General chapters (e.g. pharmaceutical technical procedures) become mandatory when referred to in a monograph

GENERAL MONOGRAPHS

apply to **all** substances and preparations within the scope of the definition section of the general monograph, except where a preamble limits the application.

Substances and preparations that are the subjects of **individual monographs** are required to comply with relevant, applicable general monographs

GENERAL MONOGRAPHS ON DOSAGE FORMS

- apply to all preparations of the type defined
- requirements not necessarily comprehensive but additional may be imposed by competent authority

Headings of Dosage form monographs

- Definition
- Production
- Tests
- Storage

Parenteral preparations

Definition Sterile preparations intended for administration by injection, infusion or implantation into the human or animal body

- injections (*non-/aqueous: solution, emulsion, suspension*)
- infusions (*aqueous: solution, emulsion*)
- concentrates for injections or infusions (*solution*)
- powders for injections or infusions (*forms solution or suspension*)
- implants (*solid of suitable size and shape*)

Parenteral preparations- Production section

- instructions to manufacturers
- statements cannot necessarily be verified on a sample of final product by independent analyst

e.g. efficacy of anti-microbial preservation, methods of preparation of sterile products, water for injections, test for extractable volume)

Mandatory tests

- **All types:** particulate contamination:sub-visible particles, sterility
- **Injections:** + UoC, bacterial endotoxins-pyrogens
- **Infusions:** + bacterial endotoxins-pyrogens
- **Concentrates:** + see infusions
- **Powders:** + UoC, UoM, bacterial endotoxins-pyrogens
- **Implants:** -

Mandatory test methods (referred to in monograph on parenteral preparations)

- 2.6.1 Sterility
- 2.6.8 Pyrogens
- 2.6.14 Bacterial endotoxins
- 2.9.5 UoM
- 2.9.6 UoC
- 2.9.19 Particulate contamination:sub-visible particles

General notices (Ph.Eur.)

“With the agreement of the competent authority, alternate methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.”

Storage

...do not constitute a pharmacopoeial requirement but the competent authority may specify particular storage conditions that must be met.

NOTICE TO APPLICANTS Application form SPC, labelling and package leaflet

- Pharmaceutical form (*use current list of standard terms-Ph.Eur*)
- Route(s) of administration (*use current list...*)
- Container, closure and administration device(s)... (*use current list...*)

Standard terms

- used in specific sections of EU application format for medicinal products
- basic terms needed to characterise a pharmaceutical form
- definitions and requirements given in general monographs of dosage forms

- Three standard term lists:

1/ pharmaceutical forms 2/ routes of administration 3/ containers, closures and administration devices

- Product specific terms:

combination of standard terms or elements of such

- Short terms:

for labelling of medicinal product only

**Parenteral preparations:
Pharmaceutical form**

- Solution for injection
- “ “ “ , cartridge
- “ “ “ , pre-filled syringe
- “ “ “ , pre-filled pen
- Solution for injection for subcutaneous use
- Powder for solution for injection
- Powder and solvent for solution for injection
- “ “ “ “ “ “ “ “ ,pre-filled pen

Short terms for labelling

- Injection instead of e.g. solution for injection
- Powder for injection powder for solution for injection
- Sterile concentrate concentrate for solution for injection
- Intravenous infusion solution for infusion

In summary

European Pharmacopoeia, Standard terms and Regulation (authorisation and supervision) procedures for medicinal products are in a joint structure guaranteeing the quality of medicines to public health.

International Harmonisation of Q6A items

- Disintegration
- Dissolution
- Uniformity of dosage units

Status & Implications

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Levels of harmonisation

- Equipment dimensions
- Test conditions
- Acceptance criteria

2

Disintegration – Stage 5B sign-off June 2004 (small tablets)

- Equipment harmonised
- Volume: to be adapted to prevent units floating out the tubes
- Disks: - only where specified or allowed
- allowed for electronic endpoint detection
- Temp: $37 \pm 2^{\circ}\text{C}$
- Criteria: 6 of 6 meet stage 1
16 of 18 meet stage 2

For large tablets, Ph. Eur. has adopted the USP method (outside IH)

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Dissolution of solid oral dosage forms Stage 5B sign-off June 2004

Equipment: 4 types:

1. basket
2. paddle
3. reciprocating cylinder
4. flow-through cell

- essentially harmonised (1 l vessel for app. 1 and 2)
- reciprocating cylinder not accepted by JP

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Dissolution of solid oral dosage forms

Test conditions:

- temp 37 ± 0.5 °C
- sampling with/without repletion both allowed
- volume: $\pm 1\%$ for basket & paddle
- sequential testing not accepted by JP

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Dissolution of solid oral dosage forms

System suitability criteria:

- conformance to dimensions and tolerances
- volume & temp. dissolution medium
- rotation speed (app. 1 and 2) $\pm 4\%$
- dip rate (app. 3) $\pm 5\%$
- flowrate (app. 4): $\pm 5\%$

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Dissolution of solid oral dosage forms

Acceptance criteria:

- harmonised, except for sequential testing
- S3 also accepted in Europe, as OC-curve nearly identical with S2

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Dissolution of solid oral dosage forms

Not harmonised items:

- sequential testing not accepted by JP
- reciprocating cylinder not accepted by JP
- no list of media (from EU task force)
- recommendations for dissolution testing are lacking (Ph. Eur. regional text)
- pooled samples not accepted by Ph. Eur.
- calibrator tablets not accepted by Ph. Eur.

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**Uniformity of Dosage Units
Stage 5B signed 18 Feb 2004
Harmonised Method**

Dosage Unit :

a dosage form containing a single dose or a part of a dose of an active substance

Uniformity of D.U. :

degree of uniformity in the amount of the active substance among dosage units

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Uniformity of Dosage Units

Two approaches :
Content Uniformity
Mass Variation

C.U. is universally applicable, MV on certain conditions

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Uniformity of Dosage Units

Mass Variation is applicable for:

1. Solutions in single dose containers and in soft capsules
2. Solids (including powders, granules and sterile solids) in single-dose containers containing no active or inactive added substances
3. Solids (including sterile solids) in single-dose containers, with or without active or inactive added substances, prepared from true solutions and freeze-dried in the final containers

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Uniformity of Dosage Units

Mass Variation is applicable for:

4. Hard capsules, uncoated or film-coated tablets, containing ≥ 25 mg of an active substance comprising $\geq 25\%$ by mass of the dosage unit or the capsule contents (ICH agreement, 10% of mass was not a viable option)
5. Products not meeting the 25 mg/25% threshold limit but having a concentration RSD of the active substance $\leq 2\%$, and having regulatory approval for this approach. (USP and JP limit this to item 4 products)

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Uniformity of Dosage Units

Method content uniformity:

- select 30 dosage units & analyse first 10
- calculate Acceptance Value:

M = Reference value, in % of label claim:
depends on \bar{x} and T

\bar{x} = mean value of individual contents as % of label claim

T = target amount at time of manufacture

k = acceptability constant: $n = 10 k = 2.4$
 $n = 30 k = 2.0$

s = sample standard deviation

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Uniformity of Dosage Units

Acceptance criteria:

$n = 10 \quad AV \leq 15.0$

$n = 30 \quad AV \leq 15.0$ and
0 units $< 0.75 M$ or $> 1.25 M$

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Uniformity of Dosage Units

Method Mass Variation

- perform batch assay to obtain A in % of label claim
- select 30 dosage units and weigh first 10
- determine individual estimated contents by

x_1, x_2, \dots, x_n = individual estimated contents of the dosage units

w_1, w_2, \dots, w_n = individual masses of the dosage units

\bar{w} = mean of individual masses

- proceed as under content uniformity

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Uniformity of Dosage Units

Major changes compared to current approach:

- test by variables instead of by attributes
- increase of threshold from 2 mg/2% to 25 mg/25%
- expression in % label claim instead of average assay (JP: 1998 "Therapeutic effects of each unit are expected for the label claim")

Notes:

- UDU pertains to release and end of shelf life
- UDU pertains to parts of tablets for which subdivision is authorised

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Uniformity of Dosage Units

Harmonised Method measures 2 different features of a product:

- degree of uniformity, which is constant for a particular batch of product and related to the manufacturing process
- degradation rate resulting in a declining value for

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Uniformity of Dosage Units

Failure is possible due to degradation of the product, not due to an insufficient degree of uniformity, on which the focus should be.

Conclusion: Approach is a scientifically flawed hybrid. Normalisation would have compensated this flaw, but was politically inachievable.

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Uniformity of Dosage Units

Example for maximally acceptable s
at $\bar{X} = 90\%$ and $M = 98.5\%$
(no overage at manufacture)

$n = 10$ $s = 2.71\%$ LC $rsd = 3.0\%$
 $n = 30$ $s = 3.25\%$ LC $rsd = 3.6\%$

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Uniformity of Dosage Units

Taking into account that a sample is taken,
whereas we wish to state something about
the population (= batch), for 95%
probability of passing: $\bar{X} < 2.1\%$ of LC.

Might be problematic for very low dosed and
for dry-mixed products. Compared to
currently approved % rsd (USP 6.0 and
7.8%) the new test is roughly twice as
strict.

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Uniformity of Dosage Units

Transitory arrangements

Ph. Eur.

- UDU for products yet to be authorised
(July 2005)
- old approach for current products
- assay at release: 95-105% of label claim
- c.u.: 85-115% ($n=10$) of average assay

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Uniformity of Dosage Units

Transitory arrangements

EMA/QWP:

- change in x years to UDU for existing products via type II variation
- ask industry for comments/end of shelf life data
- test marketed products according to new approach
- have implementation policy ready by 01 January 2006

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Physical Quality of Solids and Powder Characterization Techniques

Michel Veillard

Department of Pharmaceutical Sciences
Paris Research Center – Aventis Pharma

Quality on the move – EDQM – Budapest – Hungary

Definition of DS Physical Quality

The physical quality of a Drug Substance is determined by the following factors :

- the chemical structure - free base, free acid, a salt, or a neutral molecule,
- the hydration and/or solvation state,
- the solid-state (polymorphic) form present
- the amount of amorphous (detectable) content present,
- the powder properties - particle size distribution, specific surface area, morphology, density, flow characteristics, etc.

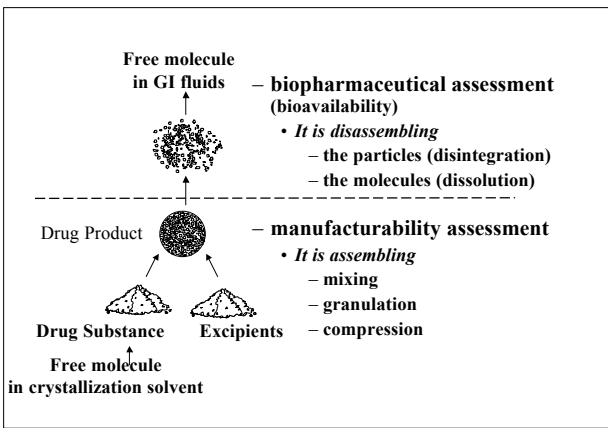
Criticality of DS Physical Quality

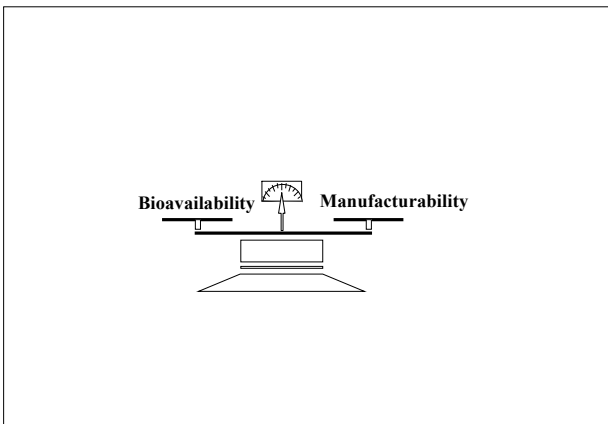
The DS physical quality is critical with regards to the following performances :

- the physical and chemical stability of the API,
- the processability of the formulation (e.g., % content of active ingredient, powder mix homogeneity, blend flowability, compressibility, excipient composition, etc.
- the dissolution properties and bioavailability of the API when present in the formulation (e.g., tablet).

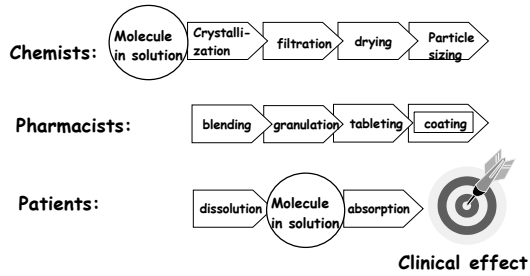
- The **tablet** is taken as example but many points can be adapted to the development of an other Pharmaceutical Dosage form.



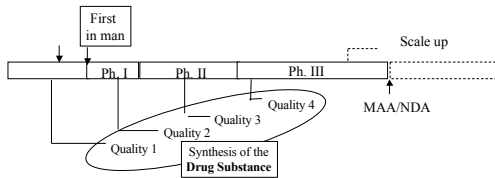


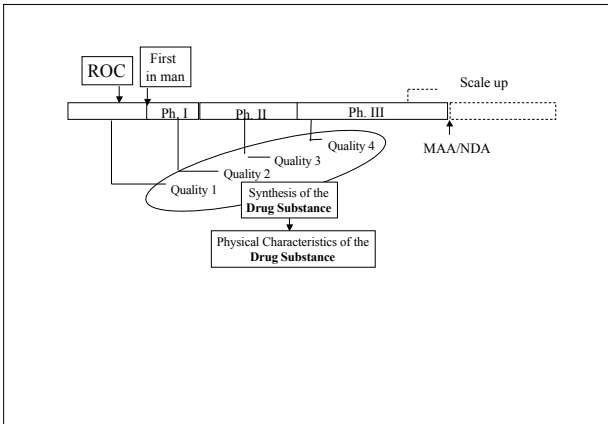


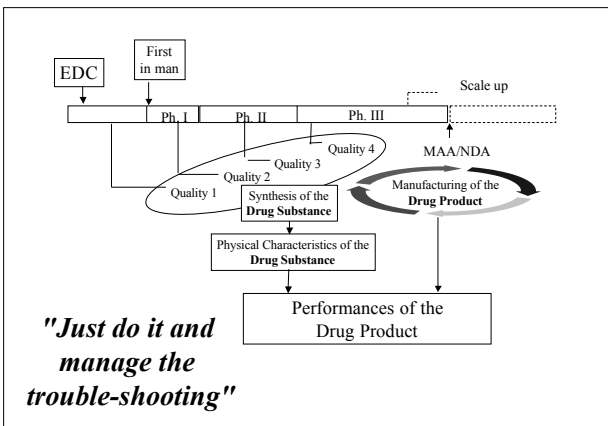
“Solid Chain”

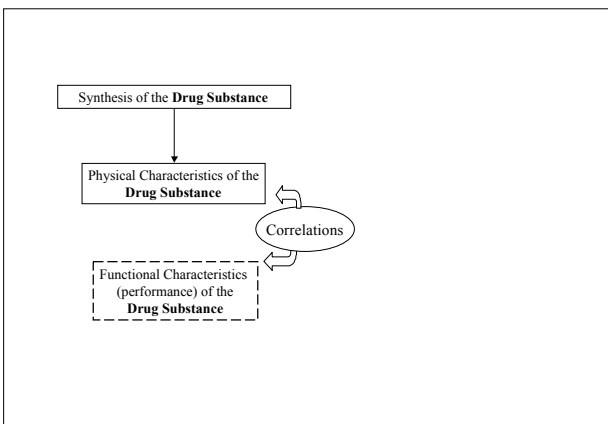


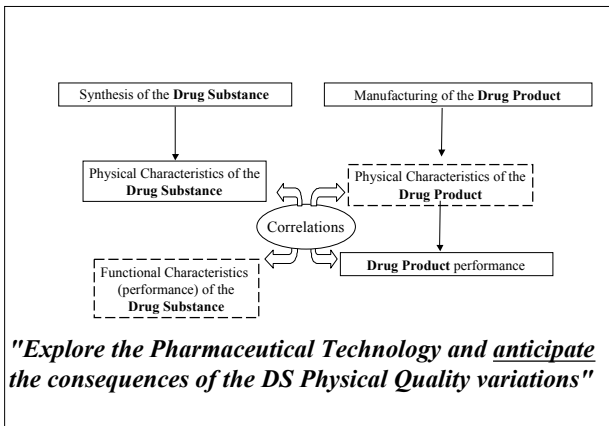
Correlations between **Drug Substance**
Physical Characteristics
and
Drug Substance/Drug Product
performances.

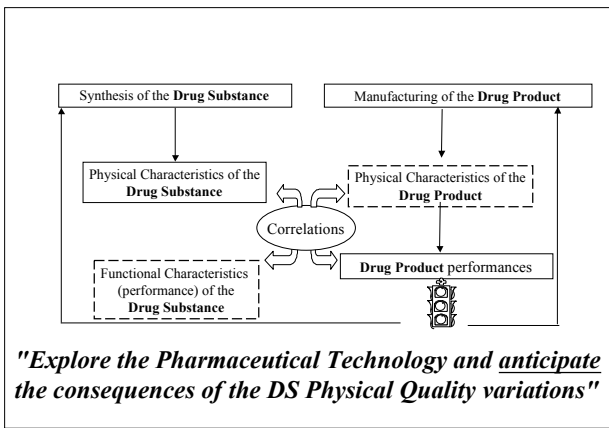












Powder Characterization Techniques

Powder Characterization Techniques have been generated from **three parallel sources** :

Techniques generated by Group 12 before the creation of EP Powder Working Group (1999)

Techniques described in USP and recently proposed to Group 12 and Powder Working Group for harmonization

Techniques generated by EP Powder Working Group with a prospective EP-USP-JP harmonization approach

Examples of EP techniques generated by Group 12 before the creation of EP Powder Working Group (1999)

- Density of Solids
- Specific Surface Area by Gas Adsorption

The texts of these two techniques are available to the European Pharmacopoeia Reader

Examples of Techniques described in USP and recently proposed to Group 12 and PWG for harmonization

- Optical microscopy
- Particle size distribution by analytical sieving
- Powder flow
- Powder fineness, Etc

The texts of these techniques will be reviewed by the EP Powder Working Group and Group 12 before to be made available to the European Pharmacopoeia Reader

Techniques generated by EP Powder Working Group with a prospective EP-USP-JP harmonization approach

First Set of Techniques (initiated in 1999)

- 1- Particle size analysis by laser diffraction (Oct 04),
- 2- Porosity and pore size distribution of solid materials by mercury porosimetry (Jan 04),
- 3- Characterization of crystalline solids by X-ray powder diffraction (Oct 04),

The texts of these three techniques are well advanced and are published (or planned to be) in Pharmeuropa and sent to the PDG (stage 4)

Techniques generated by EP Powder Working Group
with a prospective EP-USP-JP harmonization approach

Second Set of Techniques (initiated in 2002)

- 1- Gravimetric water sorption (Dec 04)
- 2- Microcalorimetry (Preliminary stage)
- 3- Wettability of powders (Very preliminary stage)

The text of the technique «Gravimetric water sorption »
is planned to be published in Pharmeuropa
and sent to the PDG (stage 3)

Characteristics $\xrightarrow{\text{Property}}$ Performance

Physical and chemical characteristics	Property	Performance
Particle size distribution Maximum solubility Wettability Texture of the powder	Soluble (at neutral pH)	> 80 % dissolution after 10 minutes in phosphate buffer pH 7.4

Scientists deals with characteristics and
properties (mechanisms)

Authorities deal with performances (phenomena)
and validation (statistics)

Conclusion

1- Powder Characterization Techniques should be made available in the same format to the Scientists by all Pharmacopeia as General Chapters

2- Correlations between Drug Substance and Drug Product Performances with the Characteristics/Properties of the Drug Substance are to be studied and reported to Authorities.

2- The Powder Characterisation Techniques are chosen as a function of their ability to help such correlations to be established.

EP Powder Working Group reports to Group 12

Chairman : Michel Veillard – France
EDQM : Isabelle Mercier

Members :

Mikael Bisrat – Sweden
Edgar John – Switzerland
Jan Karlsen – Norway
Christophe Laroche – UK
Franck Leveiller – Sweden
J. Norwig – Germany
Michael Mutz – Switzerland
Juhani Posti – Finland
Magali Sautel – France
Jeannot Schelcher – Switzerland

Back-Up Slides

**Particle size analysis by laser diffraction
What does it contain ? Part I**

- Introduction**
- Principle**
- Apparatus**
- Development of the method**
 - Sampling**
 - Evaluation of the dispersion procedure**
 - Optimisation of the liquid dispersion**
 - Optimisation of the gas dispersion**
 - Determination of the concentration range**
 - Selection of an appropriate optical model**
 - Repeatability**

**Particle size analysis by laser diffraction
What does it contain ? Part II**

- Measurement - Precautions**
- Measurement of the light scattering
of dispersed sample(s)**
- Conversion of scattering pattern
into particle size distribution**
- Replicates**
- Reporting of Results**
- Control of the apparatus performance**
 - Calibration**
 - Verification of the system**

**Characterization of crystalline solids by X-ray
powder diffraction**

What does it contain ? Part I

- Introduction**
- Principles**
- Apparatus**
 - Instrument set-up**
 - X-ray radiation**
- Specimen preparation and mounting**
 - Specimen preparation**
 - Specimen mounting**
 - Effect of specimen displacement**
 - Effect of specimen thickness and transparency**
- Diffractometer alignment**
- Calibration, Performance testing and Monitoring of
diffractometers**

Characterization of crystalline solids by X-ray powder diffraction

What does it contain ? Part II

- Qualitative phase analysis (identification of phases)
- Quantitative phase analysis
- Matrix effects
- Polymorphic samples
- Methods using a standard
- Estimate of the amorphous and crystalline fractions
- Obtaining structural information from XRPD pattern
 - Determination of lattice parameters
 - Structure solution
 - Refinement of crystal structures

Gravimetric water sorption
What will it contain ?

- Determination of sorption-desorption
- Determination of hygroscopicity
- Determination of water activity
