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Advances in Synchrotron XRPD for the Enhanced Characterization of Pharmaceuticals

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Outlook

I. Role of structural analysis in the pharmaceutical industry

II. Synchrotron Radiation X-Ray Powder Diffraction (SR-XRPD)

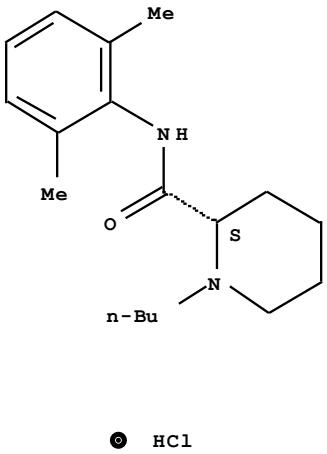
III. Synchrotron XRPD in the field of pharmaceuticals

IV. Conclusions

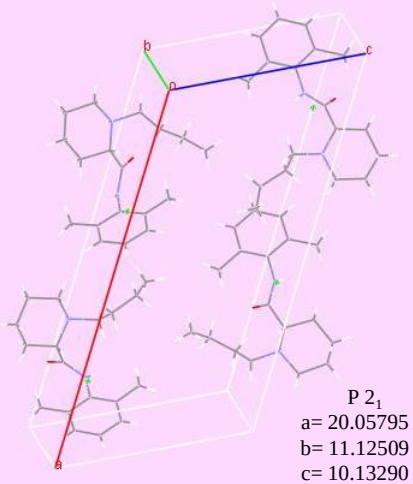
Why is structural analysis relevant to the pharmaceutical industry?

- Polymorphism and the relation between structure ↔ properties
- Microstructural properties (e.g. influence of stress and strain, particle size and domain)

Example of
Bupivacaine Hydrochloride

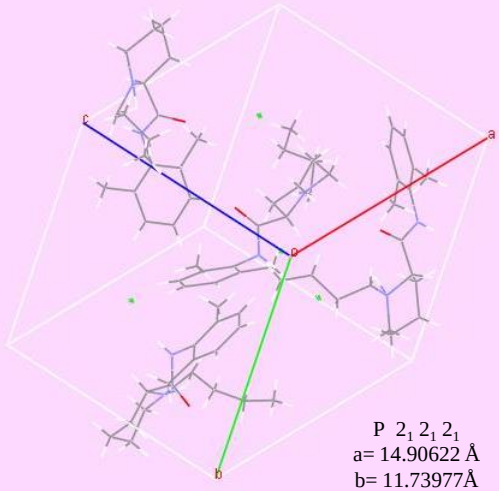


Form B at 112 °C, monoclinic



P 2_1
a= 20.05795 Å
b= 11.12509 Å
c= 10.13290 Å
b= 116.18377 °

Form D at 20 °C, orthorhombic



P $2_1 2_1 2_1$
a= 14.90622 Å
b= 11.73977Å
c= 11.08386Å

Gozzo, Masciocchi , Griesser, Niederwanger, 2010. Personal Communication

Properties influenced by the solid state structure of substances and, therefore, influenced by polymorphism:

- Solubility
- Pharmacokinetics and pharmacodynamics
- Thermodynamic properties (e.g. stability of drugs) → in-situ non-ambient time-resolved studies
- Spectroscopic properties
- Mechanical properties (e.g. hardness, compressibility, tableting, tensile strength)

Polymorphic studies play a key role throughout the whole life-cycle of products

Compound selection

- Identification and characterization of individual polymorphic forms and selection of desired form

Technical development

- Development of manufacturing processes to ensure high and reproducible content of desired polymorphic form
- Polymorphic studies for impurity detection and stability studies
- Crystal engineering (e.g. co-crystallization*)

Commercial production

- Polymorphic characterization to support (1) process validation, (2) comparability studies following process changes, and (3) investigations to assess impact of deviation on product quality

Intellectual Property (IP)

Fight against counterfeit drugs

X-ray Powder Diffraction, in particular with **synchrotron radiation** is a **unique** and **powerful** technique for such studies

* Example of carbamazepine (see *Organic Crystal Engineering*, Eds. Tiekink, Vittal & Zaworotko, Wiley 2010)

What makes **synchrotron-XRPD**

such a powerful analytical tool?

Our 3 ingredients for state-of-the-art SR-XRPD

A. An efficient synchrotron facility and beamline optics

B. State-of-the-art diffractometers

C. Outstanding detection systems

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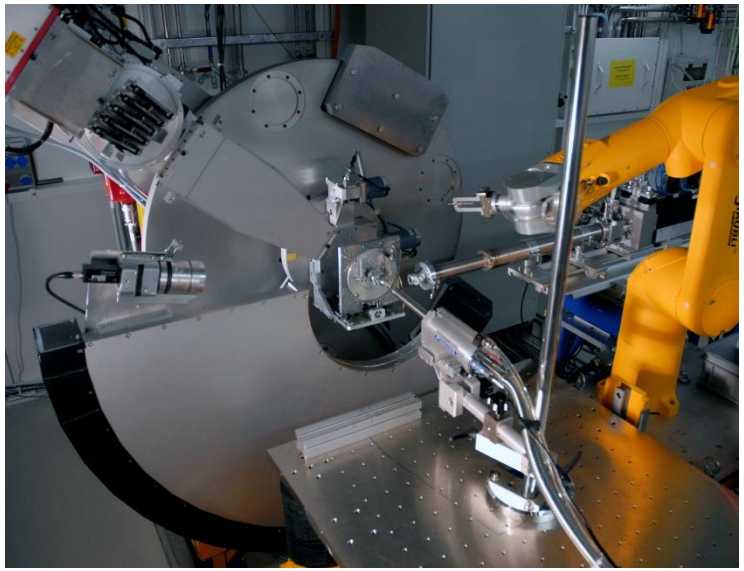


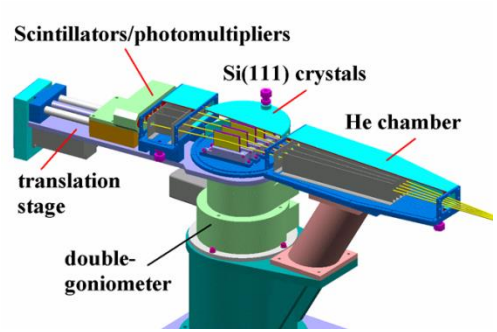
Our 3 ingredients for state-of-the-art SR-XRPD

A. An efficient synchrotron facility and beamline optics

B. State-of-the-art diffractometers

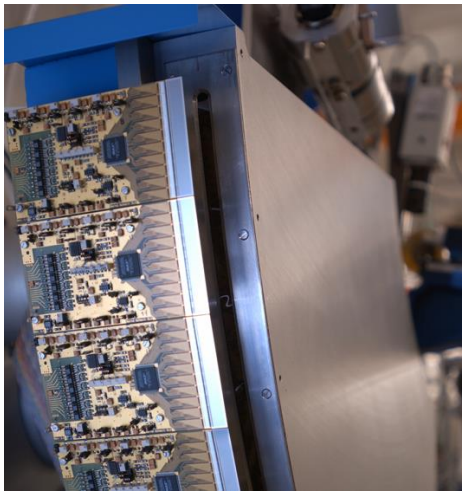
C. Outstanding detection systems

Hodeau et al, 1998



Multicrystal Analyser

Schmitt et al, 2003,
Bergamaschi, Schmitt et al, 2010



MYTHEN II

A. Synchrotron facility and beamline optics

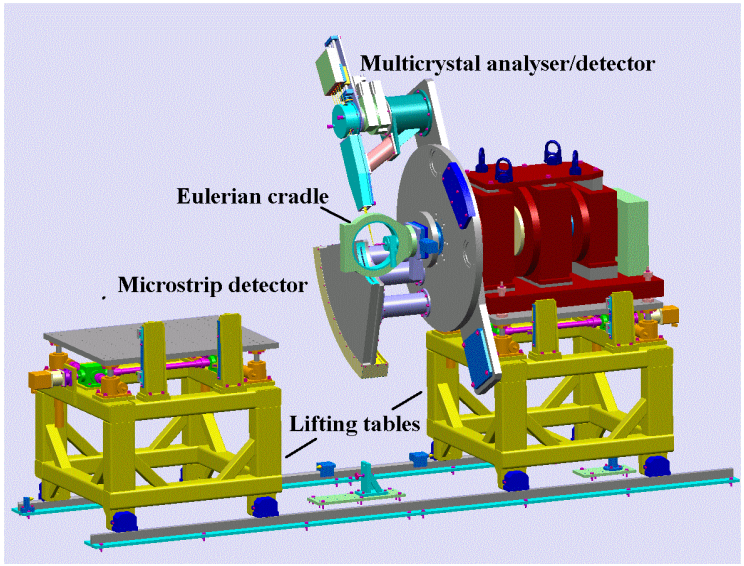
Properties:

- High Spectral Brightness: 10^{12}-10^{15} photons/sec in small beams (μm^2 to mm^2)
- Tunable and monochromatic photon energy
- Polarization
- Time structure
- Coherence

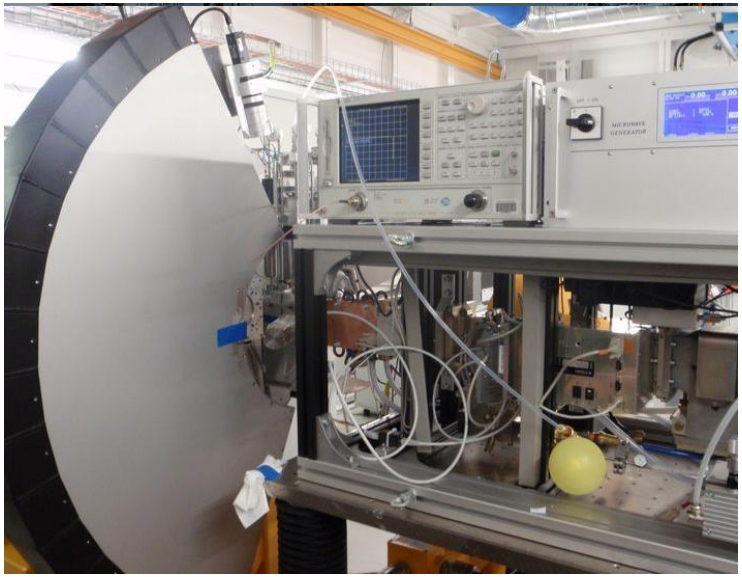
Benefits

- Efficient data collection, high statistics
- Time-resolved in-situ non ambient XRD
- Photon-consuming experimental set ups
- Penetration of highly absorbing materials
- Variable d-spacing resolution
- large unit cells (many reflections at very low angles)
- XRD near absorption edges (anomalous dispersion)

B. State-of-the-art diffractometers



Swiss Light Source-Materials Science beamline
Powder Diffraction station



Properties:

Resolution: 1 arcsec

Accuracy: ±2 arcsec

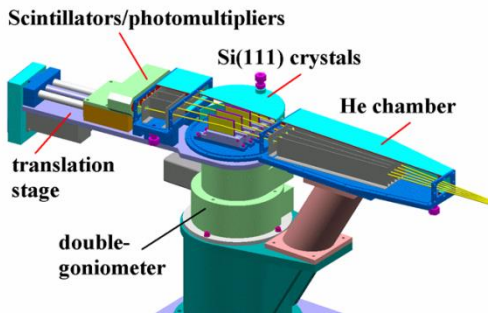
Precision: ±1 arcsec

Large working space and flexibility

Benefits

- Great mechanical stability
- Highest flexibility to accommodate all kinds of sample environments

C. Outstanding detection systems



Multicrystal Analyser

Hodeau et al, 1998

Properties:

- Angular selection of diffracted beam
- Fluorescence suppression

Benefits:

- Ultra-high resolution (better than 0.003°)
- Angular resolution independent of sample dimension and position
- Independence of transparency effect
- High S/N and S/B

Trade-off:

Long measurements (min to hours) → radiation damage

Schmitt et al, 2003,
Bergamaschi, Schmitt et al, 2010

Properties:

- Solid state modular microstrip detector
- Large dynamic range (24 bits)
- Single photon counting read out
- Fluorescence suppression
- Very fast acquisition times (subsec)

Benefits:

- 120° angular coverage at SLS
- High d-spacing resolution
- 0.004° inherent angular resolution
- Capable of simultaneously detecting strong and weak signals
- Sub-sec time resolution XRPD for in-situ kinetic studies

Trade-off:

- Resolution limited by sample dimension
- Sensitive to the uniformity of powder distribution in sample holder, granularity, statistical orientation

Synchrotron XRPD in the field of pharmaceuticals

- Indexation, structural solutions & microstructural analyses
- Fast and dose-controlled SR-XRPD
- Quantitative Phase Analysis (L.o.D, L.o.Q)
- In-situ kinetic studies

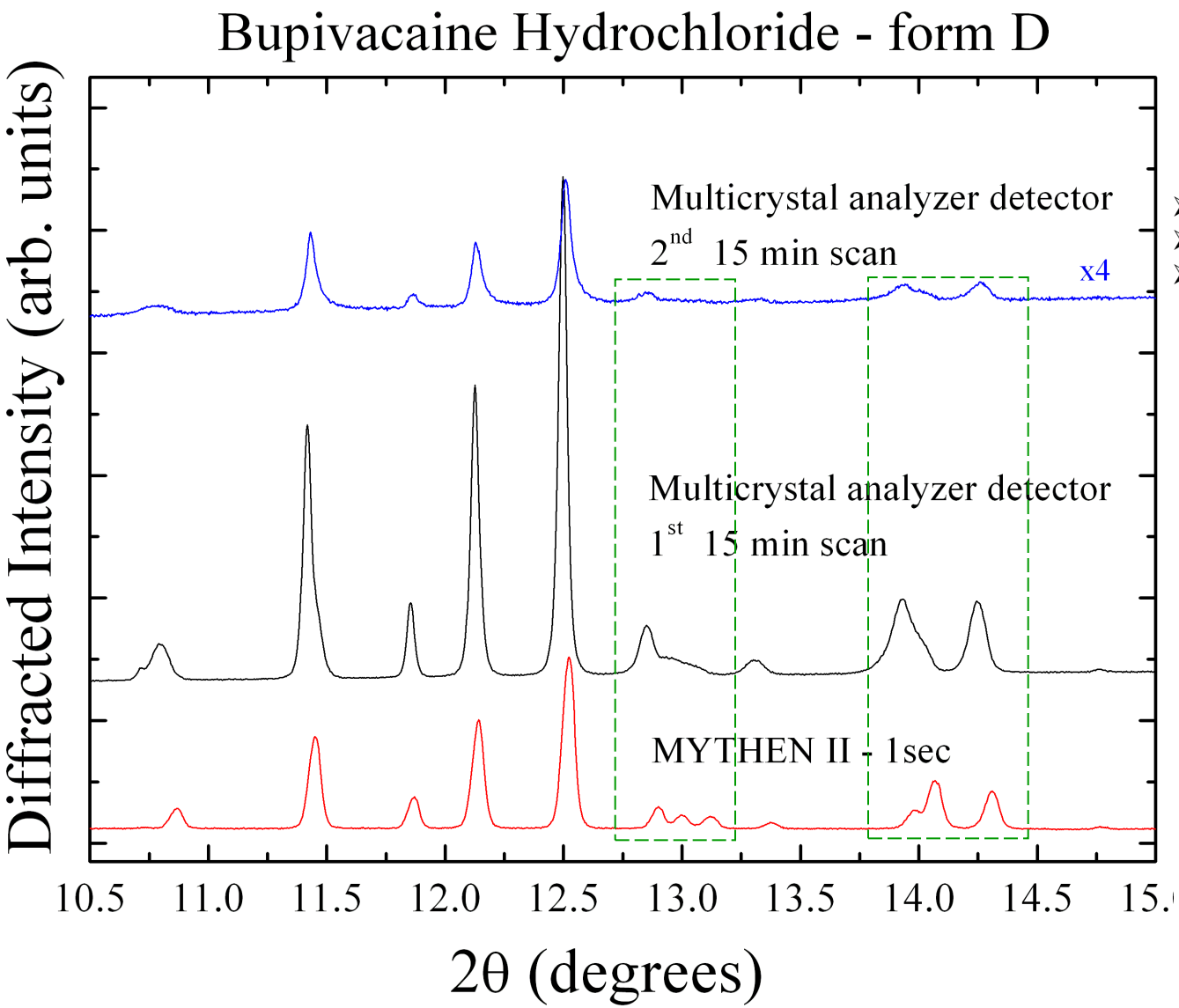
- Bruni, Gozzo et al, *Thermal, spectroscopic, and ab initio structural characterization of carprofen polymorphs*, J. Pharm. Sci.2011, **100**(6), 2321-2332
- Bergamaschi et al, *The MYTHEN detector for X-ray powder diffraction experiments at the Swiss Light Source*, J. Synchrotron Rad. (2010). 17, 653–668
- Gozzo et al, *Instrumental profile of MYTHEN detector in Debye-Scherrer geometry*, Z. Kristallogr. 225 (2010) 616–624
- Brunelli et al, *Solving Larger Molecular Crystal Structures from Powder Diffraction Data by Exploiting Anisotropic Thermal Expansion*, (2003). Angew. Chem. 115, 2075–2078.
- Graesslin et al, *Advances in exploiting preferred orientation in the structure analysis of polycrystalline materials*, J. Appl. Cryst. (2013). 46, 173–180
- Karavassili et al, *Structural studies of human insulin cocrystallized with phenol or resorcinol via powder diffraction*, Acta Crystallogr D Biol Crystallogr. 2012 Dec;68(Pt 12):1632-41

Minimization of radiation damage control with fast and dose-controlled SR-XRPD

- **Radiation Damage** is the **alteration of the structural and chemical properties** of the material under investigation induced by its exposure to electromagnetic radiation. It is **dose** and **energy** dependent
- In XRD patterns we observe shift (usually anisotropic) and broadening of reflections and their progressive disappearance → it usually undermines the success of structural solution

The effect is very serious at 3rd generation synchrotron facilities and affects the study of organic compounds, in particular pharmaceuticals

Our high-resolution, fast and dose controlled SR-XRPD measurements have opened a new gate to the systematic structural analyses of organic compounds!



- 1 mm capillary,
- Mythen data at 50% reduced intensity
- No radiation damage up to 3min

Large counting statistics
in subsec acquisition times

In-situ kinetic studies of organic compounds!

Gozzo F. , 2008
See: Bergamaschi et al, J. Synchrotron Rad. (2010). 17, 653–668

Why is Quantitative Phase Analysis relevant to the pharmaceutical industry?

- Polymorphic purity: detect and quantify unwanted polymorphic forms in both drug substance and drug product
  - Level of Detection (LoD)
  - Level of Quantitation (LoQ)
- Assess the polymorphic composition in drug substance and product
- In formulated materials, the API/excipients relative proportion is paramount and needs to be kept under control
- Degree of Crystallinity in amorphous/crystalline mixtures

- Quantification of organic compound mixtures can be achieved via different methods (e.g. spectroscopic, thermal and diffraction methods)

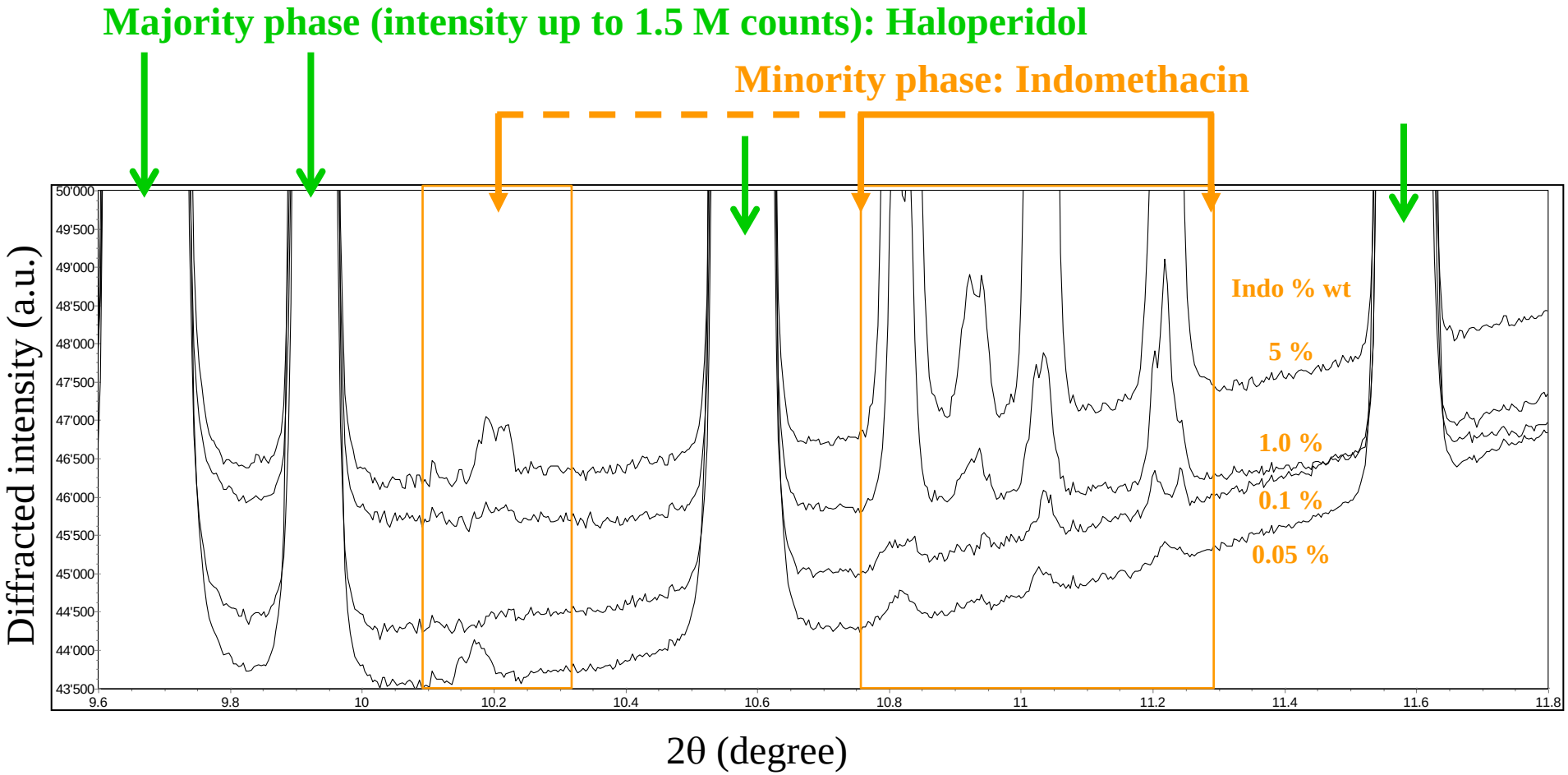
- Diffraction methods are direct methods → diffraction information is directly produced by the crystal structure of the component phases in the mixture

- Quantitative phase analysis with conventional lab-XRPD is widely used and an established practice in the pharmaceutical industry → LoD and LoQ down to very few % wt is achieved with reasonable acquisition time and powder volumes

Can SR-XRPD achieve considerably lower LoD and LoQ without increasing costs and complexity?

With our fast and dose controlled SR-XRPD we were able to **directly** detect and quantify traces of API as low as **0.05% wt** in mixtures

QPA of a binary API physical mixtures with fast SR-XRPD



- API mixtures are often characterized by an inhomogeneous distribution of the phase components

- SR-XRPD in Debye-Scherrer geometry (transmission in glass capillaries) probes relatively small powder volumes

SR-XRPD patterns were recorded at several locations on the glass capillary and the effect on the accuracy of our QPA was studied

Whole-patterns QPA Methods

➢ Rietveld Method

Rietveld, JAC (1969). 2, 65
Hill & Howard, JAC (1987). 20, 467-474

- *all phases should be crystalline and a valid structure model available for all phases in the mixture*
- *amorphous or unknown phases quantified as a group by generating absolute phase abundances for the analyzed phases (e.g. internal standard)*

➢ Rietveld-like Methods (PONKCS and Quanto+)

NO structural model required!

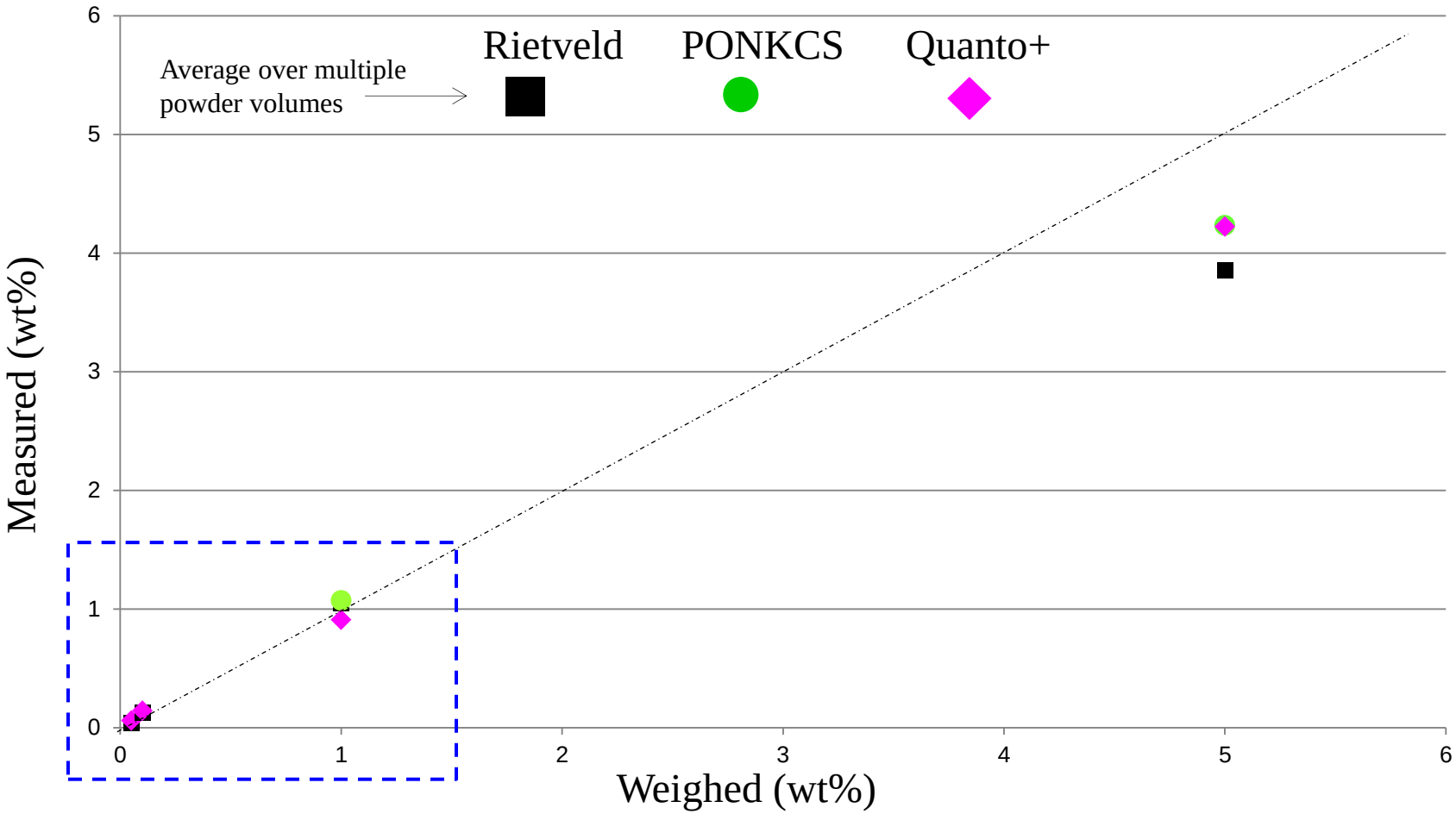
Scarlett & Madsen, Powder Diffr. 21(4), 2006, 278-284
Giannini, Guagliardi & Mililli, JAC (2002). 35, 481-490

→ *real structure factors substituted with empirical values derived from whole patterns refinement on pure phases*

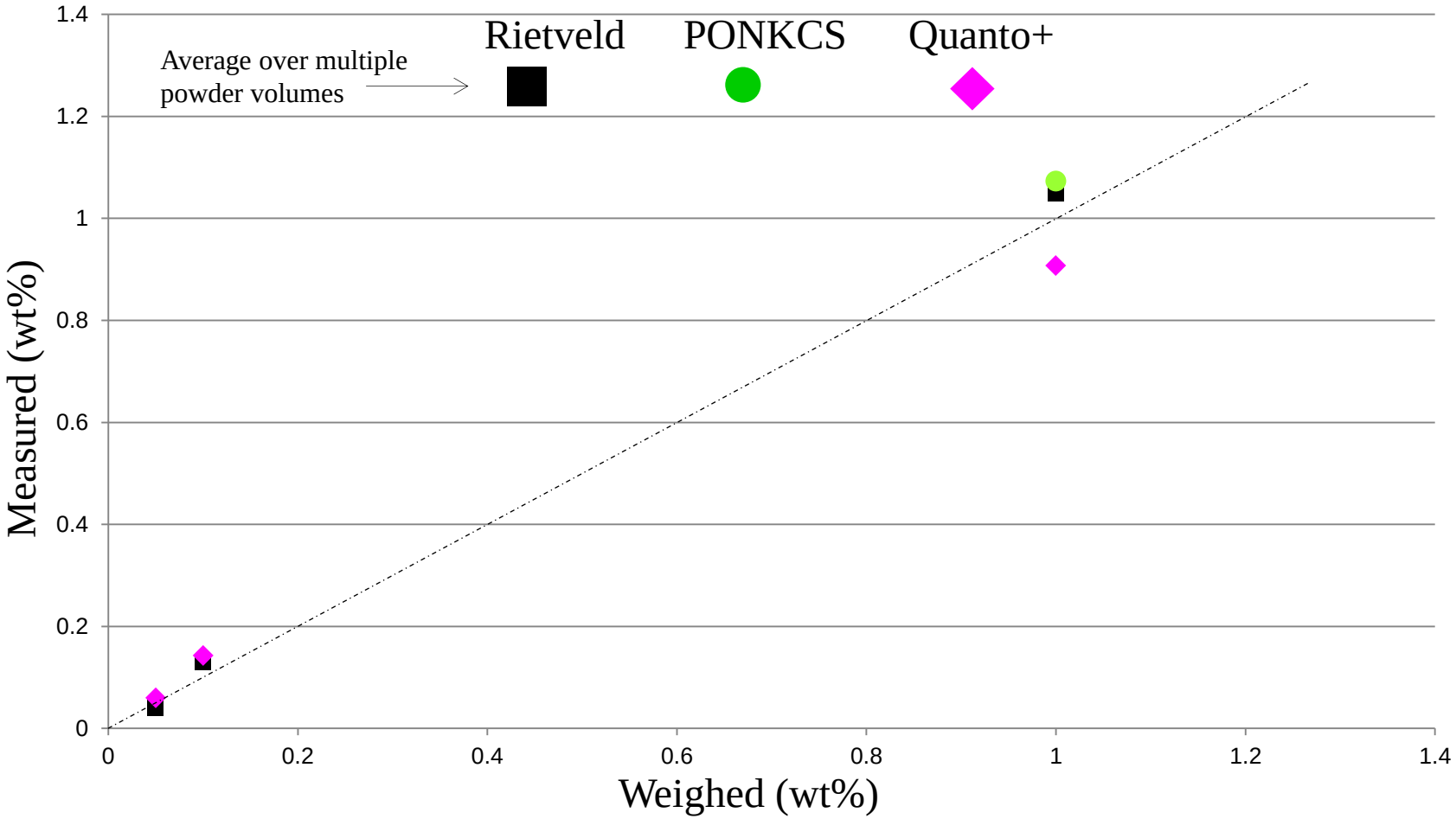
Requirements: *pure phases available (PONKCS & Quanto+), spiked pure phases (PONKCS)*

Benefits: *Rietveld-like QPA with only partial structural knowledge (PONKCS & Quanto+), with NO structural knowledge (PONKCS), application to amorphous materials (PONKCS)*

Whole-pattern QPA refinements on very diluted API mixtures

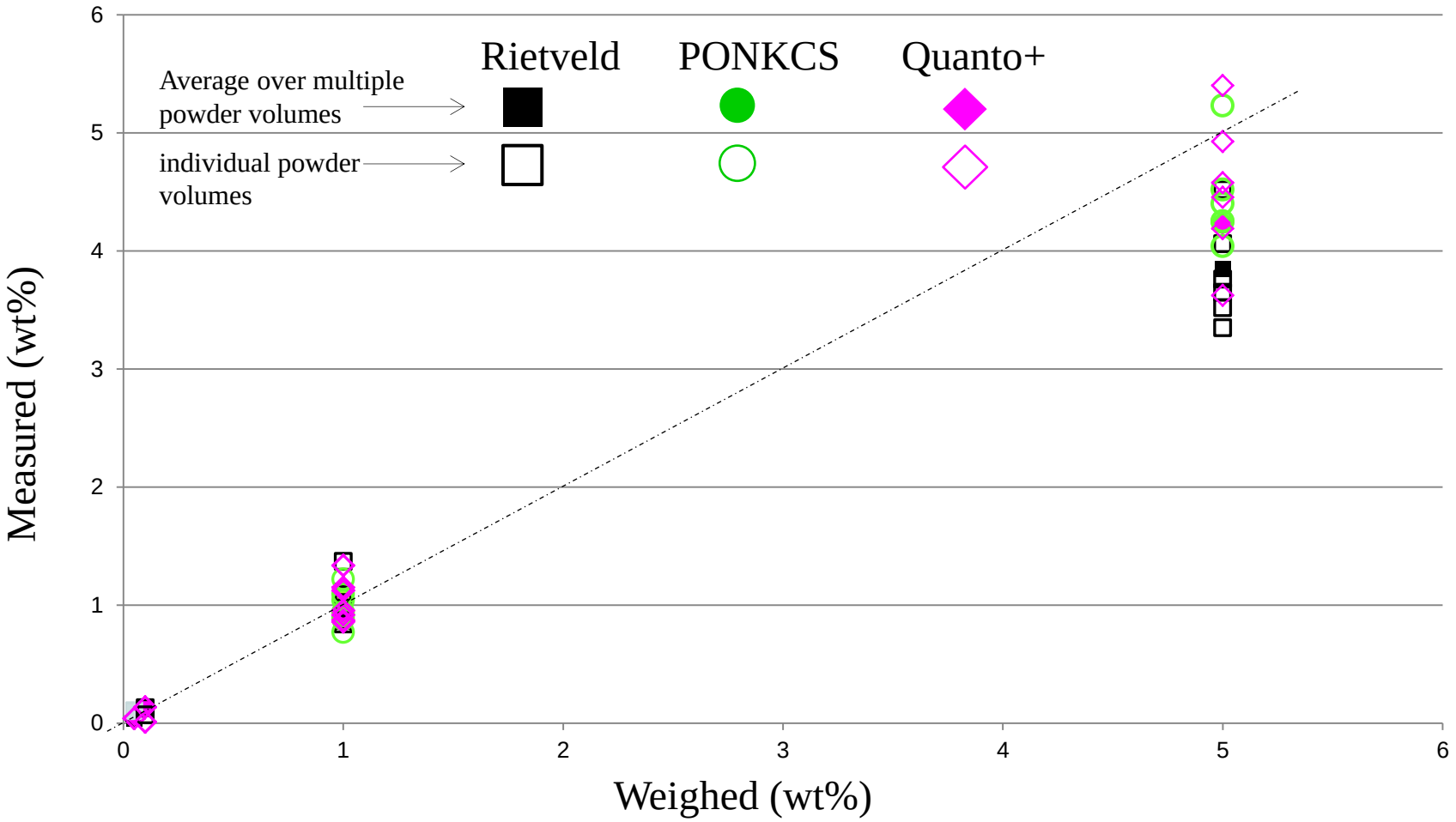


Whole-pattern QPA refinements on very diluted API mixtures



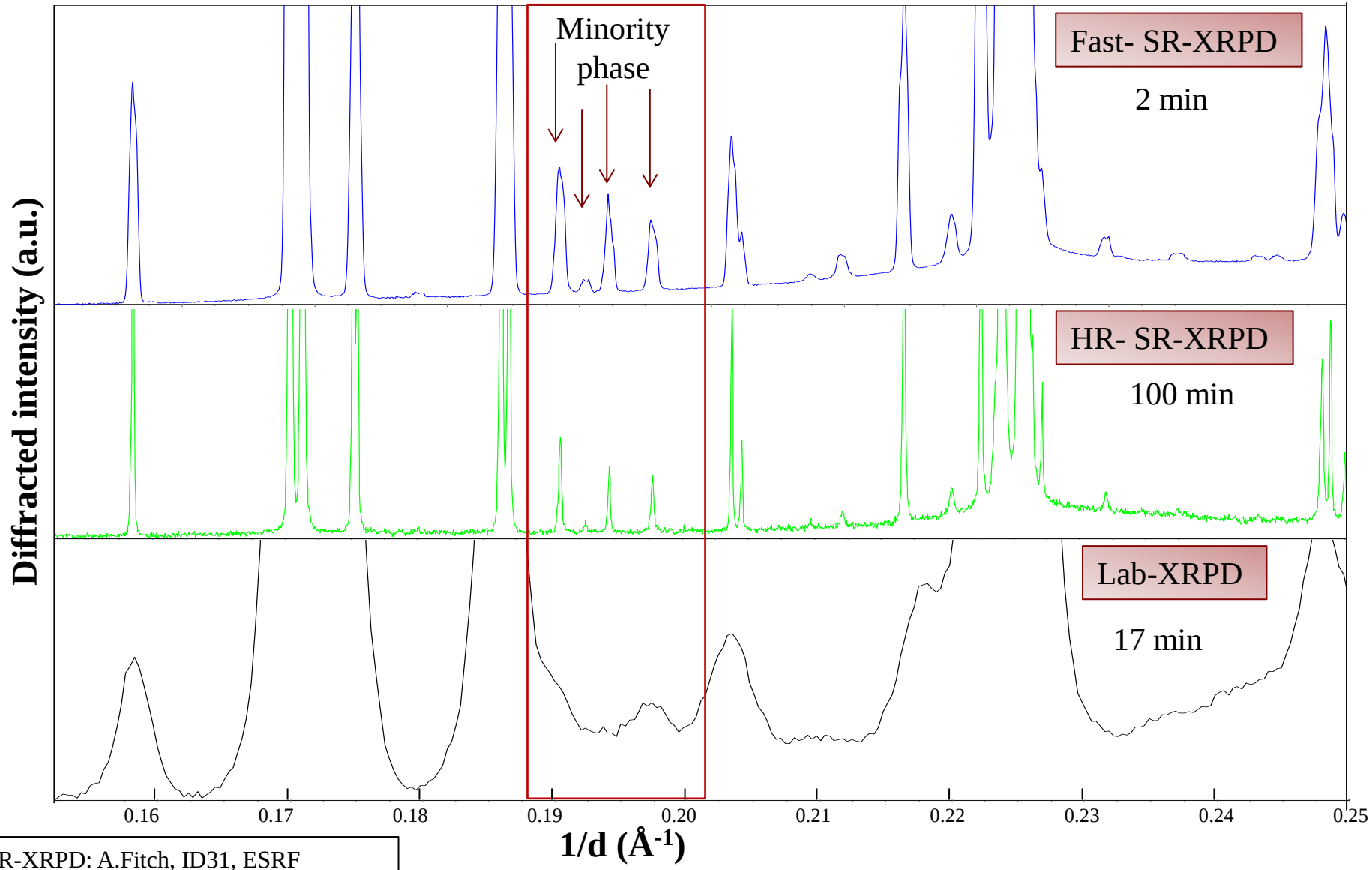
The average of %wt values at individual capillary powder volumes was consistent with %wt values from merged diffraction patterns

Whole-pattern QPA refinements on very diluted API mixtures



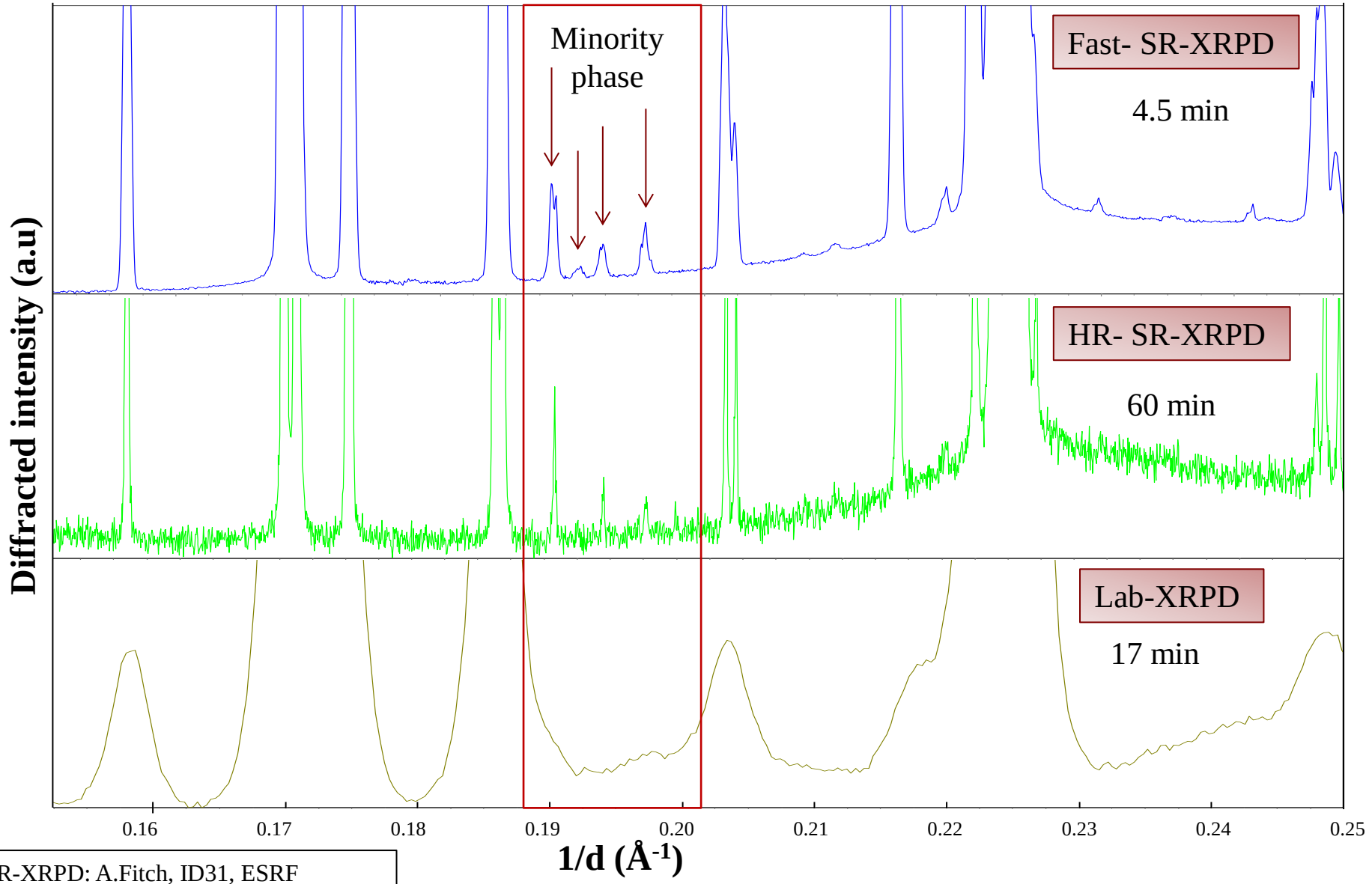
The average of %wt values at individual capillary powder volumes was consistent with %wt values from merged diffraction patterns

5% Indomethacin + 95% Haloperidol



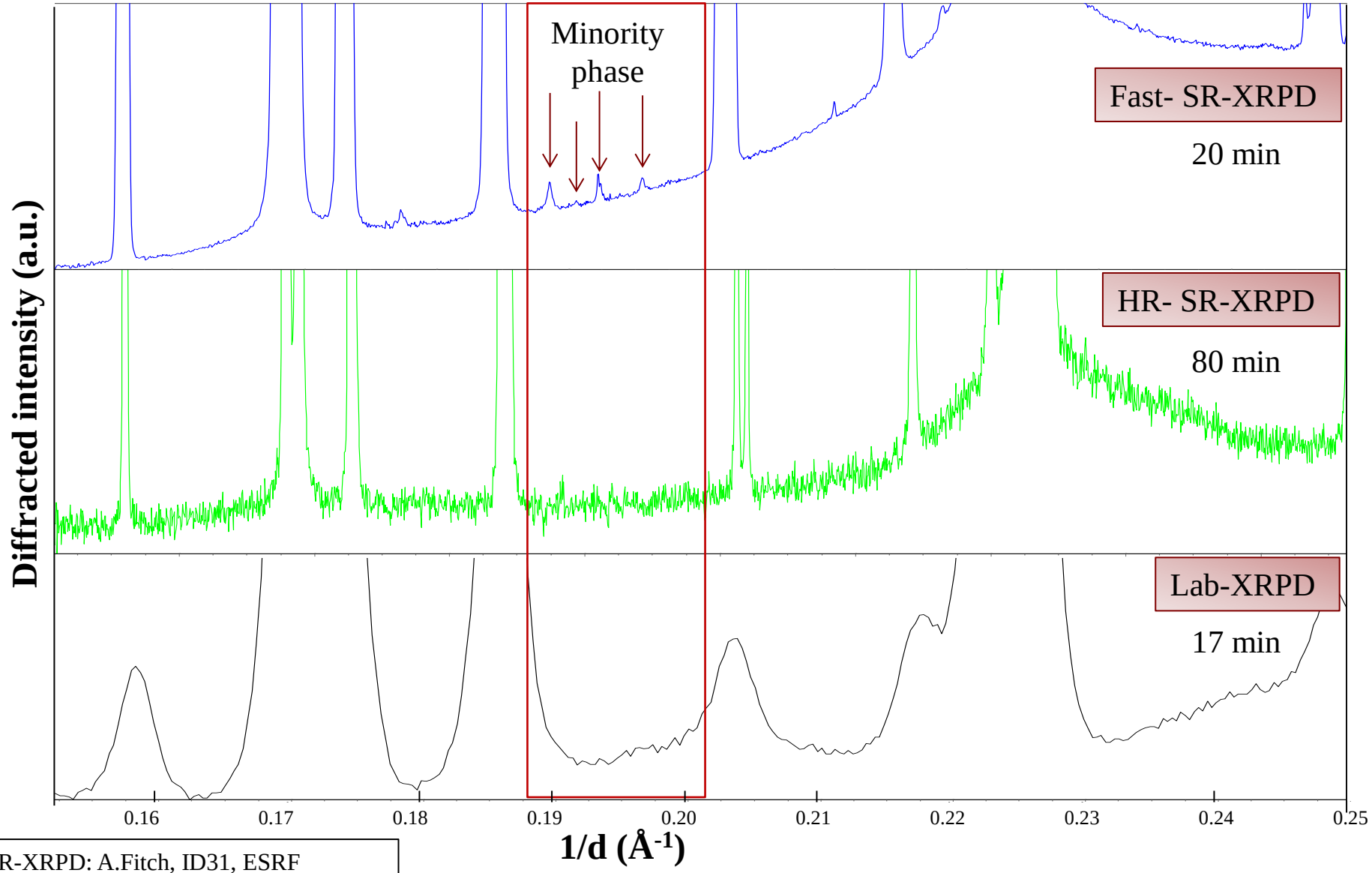
HR-XRPD: A.Fitch, ID31, ESRF
Lab-XRPD: I. Madsen, CSIRO, Australia

1% Indomethacin + 99% Haloperidol



HR-XRPD: A.Fitch, ID31, ESRF
Lab-XRPD: I. Madsen, CSIRO, Australia

0.05% Indomethacin + 99.95% Haloperidol



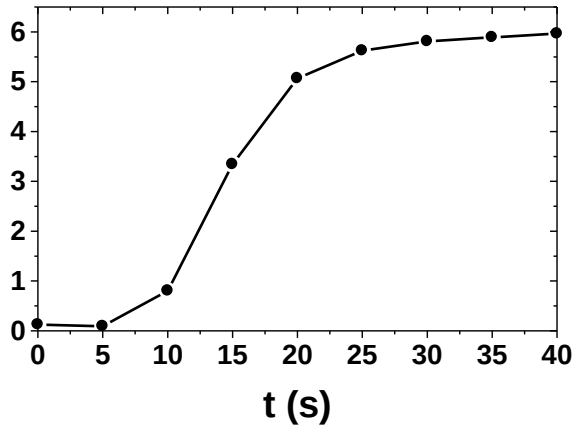
HR-XRPD: A.Fitch, ID31, ESRF
Lab-XRPD: I. Madsen, CSIRO, Australia

In-situ dynamic study of the $LaNi_5$ hydrogen absorption process

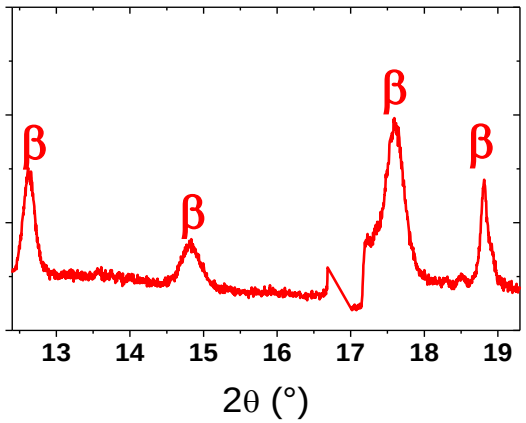
- *In-situ* hydrogen absorption at 15 bar
- *In-situ* desorption by connecting the cell to a vacuum pump
- Continuous measurements using the μstrip detector while the reaction takes place
- Acquisition times between 5 and 20 sec per pattern, depending on the reaction kinetic.

Courtesy of Prof. Cerny, Uni. Geneva - Joubert et al. Acta Materialia, **54** (2006), 713-719

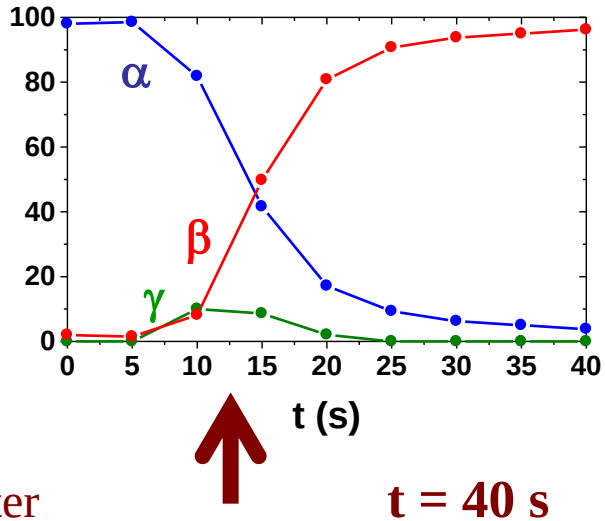
hydrogen uptake



diffraction pattern



phase content



New beamline optics+ Mythen II → 10 faster

t = 40 s

- Polymorphic forms may have a significant impact on the **quality** or **performance** of pharmaceutical and chemical products
- For pharmaceuticals, a careful characterization of the polymorphism of substances and drug product should therefore play a key role throughout the **whole life-cycle** of products
- Polymorphic studies have also started to play a key role during **patent litigations** and in the fight against **counterfeit drugs**
- Synchrotron-Radiation Powder Diffraction has become a **unique and very powerful tool for polymorphic studies**, such as kinetic analyses, the identification of closely related polymorphic forms and high-sensitivity quantitative phase analyses
- This use is in line with the regulatory expectations (ICH guidelines and FDA guidance) that newly available analytical technologies are used for **continuous improvements** in process understanding and product characterization

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- **Ian Madsen & Nikki Scarlett** for the lab-XRPD data and support for the QPA analyses, CSIRO, Australia
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