ANALYZING AMORPHOUS AND NANOCRYSTALLINE MATERIALS BY FULL PATTERN ANALYSES

T. G. Fawcett, S. N. Kabekkodu, K. Zhong, A. M. Gindhart,
J. R. Blanton and T.N. Blanton
International Centre for Diffraction Data, Newtown Square, PA, USA

This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Dear Reader,

Several comments had been added to this presentation that were not part of the original presentation but were part of the dialog accompanying the presentation. These are in red highlighted boxes.

The graphics produced in the presentation are part of the software display of the PDF-4/Organics database.

Analyzing Amorphous Materials

- Modeling
  - Random Walk – Simon Bates
  - Debye Scattering Functions –Jim Kaduk (GSAS)
- Standard Addition
  - Simon Bates, Lian Lu
  - Ann Newman
  - Shawn Yin
  - Arnt Kern (PONCKS)
- Reference Patterns – Whole Pattern Analysis
  - Cyrus Crowder
  - Tim Fawcett

Speaker presentations at prior PPXRD's see
http://www.icdd.com/ppxrd/ppxrd-presentations.htm

Methods and Tools

- Cluster Analyses with amorphous materials
  - Methods – Chris Gilmore
  - Celluloses – Tim Fawcett
  - Acetaminophen – Simon Bates
  - Lactose – Detlef Beckers (PLSR method)
- Production of Amorphous Materials
  - Thermal and Mechanical (grinding, heat and quench, hydration/dehydration)
  - Cryogrinding
  - Vapor Deposition

Speaker presentations at prior PPXRD's see http://www.icdd.com/ppxrd/ppxrd-presentations.htm

Amorphous Materials

Abstracts from PPXRD-8 - PPXRD-12 can also be browsed and searched

TOP 20 PPXRD Presentations (by Popular Download)

1. Basics of Amorphous and Amorphous Solid Dispersions
   Ann Newman, Seventh Street Development Group, Lafayette, IN
2. Particle Size Analysis by Two-dimensional XRD
   Bob He, Bruker AXS, Inc., Madison, WI
3. Amorphous Materials: A Structural Perspective
   Simon Bates, Triclinic Labs Inc., West Lafayette, IN, USA
4. Using Thermal Techniques for Amorphous Materials
   Ann Newman, Seventh Street Development Group, Lafayette, IN, USA
5. An Overview of Solid Form Screening During Drug Development
   Ann Newman, Seventh Street Development Group, Lafayette, IN
6. New Techniques for TEM - Nanoanalysis Precession Electron Diffraction for Organic – Inorganic Nanostructures
   Stavros Nikolopoulos, University of Ioannina, Ioannina, Greece
7. Making Amorphous API
   Ann Newman, Seventh Street Development Group, Lafayette, IN
8. Amorphous Solid Forms: The Use of X-ray Powder Diffraction (XRPD)
   Simon Bates, Aptuit Consulting, West Lafayette, IN
9. Diffraction, Non-Crystallinity, and the PDF Database
   Cyrus E. Crowder, ICDD, Tim Fawcett, ICDD, Newtown Square, PA
10. Characterisation and Prediction of Stability of Amorphous Materials During Pharmaceutical Development: Pair-wise Distribution Function
    Helen Blade, AstraZeneca, Macclesfield, Cheshire, U.K.

All these presentations available for free viewing at http://www.icdd.com/ppxrd/ppxrd-presentations.htm

Why Full Pattern Analysis

- Patterns are additive
- Visual
- Fast and convenient (to the user)

Multiple amorphous and nanocrystalline materials can be analyzed

Standard addition methods are preferred for accuracy and low detection limits but require multiple experimental data sets and pure standard samples.

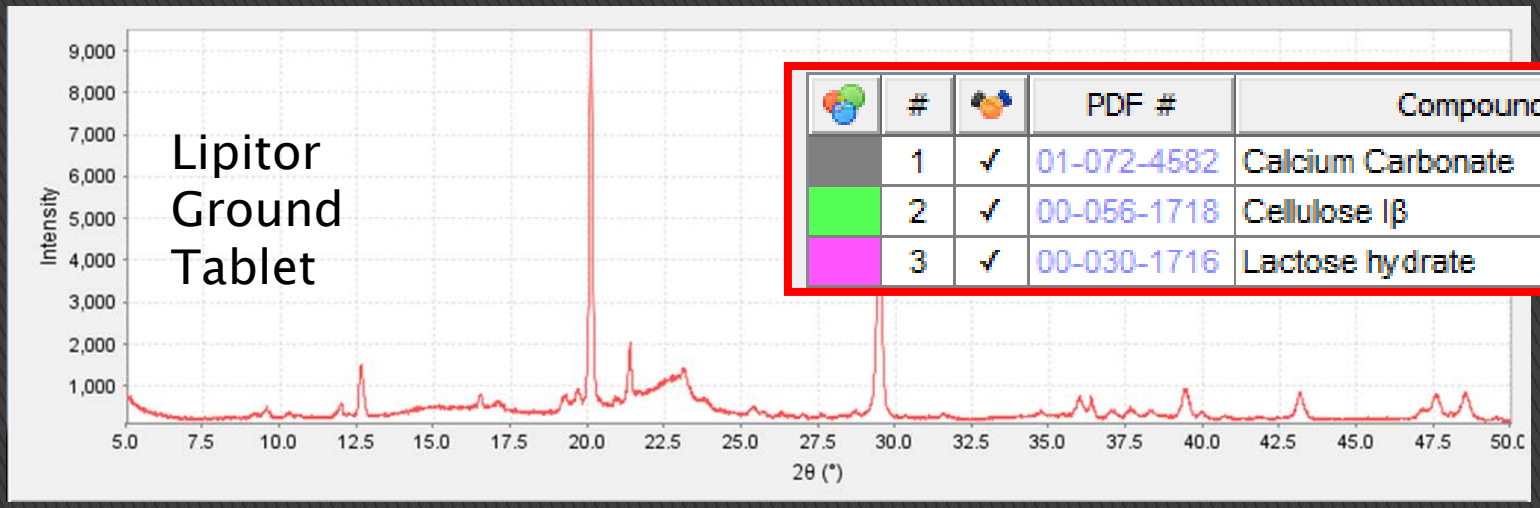
Full pattern analysis can be done on a single experimental data set using the appropriate reference data from the PDF-4/Organics database.

Five Case Histories

Full Pattern Analysis

Example I – Lipitor®

Full Pattern Analysis – Lipitor®

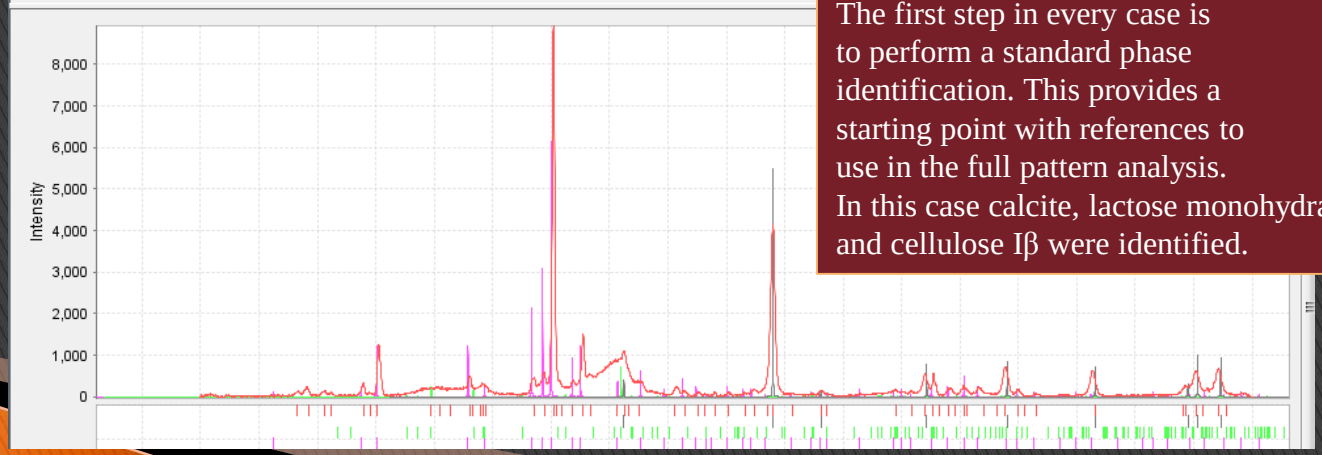


#		PDF #	Compound Name
1	✓	01-072-4582	Calcium Carbonate
2	✓	00-056-1718	Cellulose Iβ
3	✓	00-030-1716	Lactose hydrate

Identification by PDF-4/Organics Using Sleve+

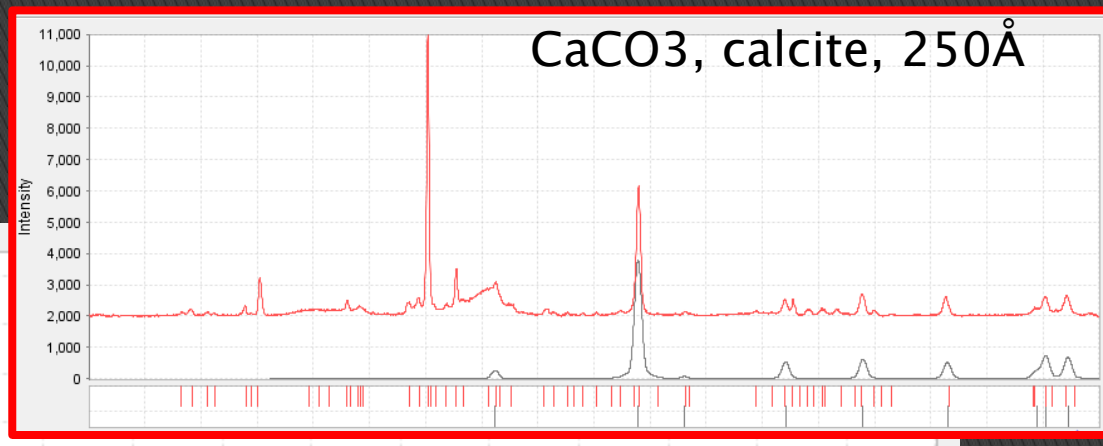
Optimize
Manually Adjust

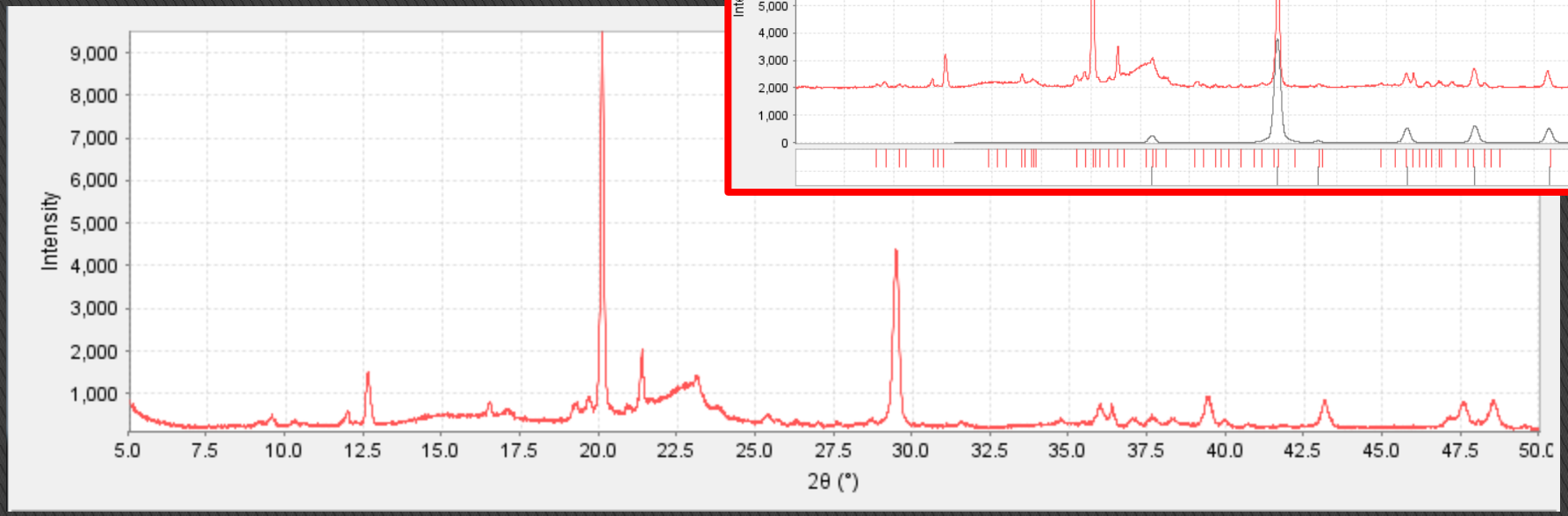
#		PDF #	Compound Name	I Ratio	I %	I/Ic	Est Wt %
1	✓	01-072-4582	Calcium Carbonate	0.610	44.526	3.23*	30
2	✓	00-056-1718	Cellulose Iβ	0.078	5.693	8.27	1
3	✓	00-030-1716	Lactose hydrate	0.682	49.781	1.55	69



The first step in every case is to perform a standard phase identification. This provides a starting point with references to use in the full pattern analysis.
In this case calcite, lactose monohydrate and cellulose Iβ were identified.

Full Pattern Analysis – Lipitor®



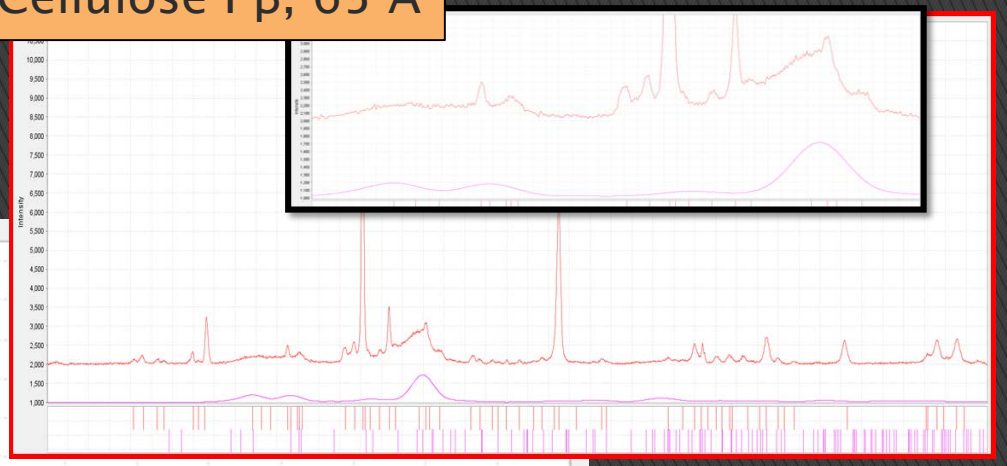


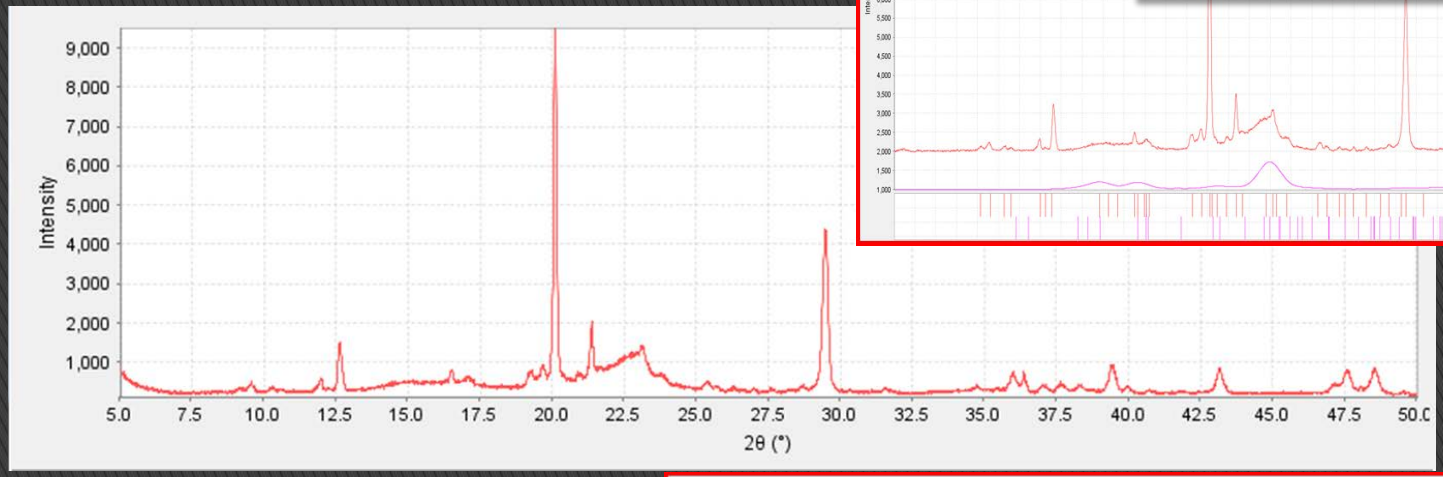
The first phase analyzed is calcite, a crystallite size program in PDF-4/Organics can be used to simulate the experimental peak shapes and identifies the crystallite size to be ~ 250 Å.

Lipitor®

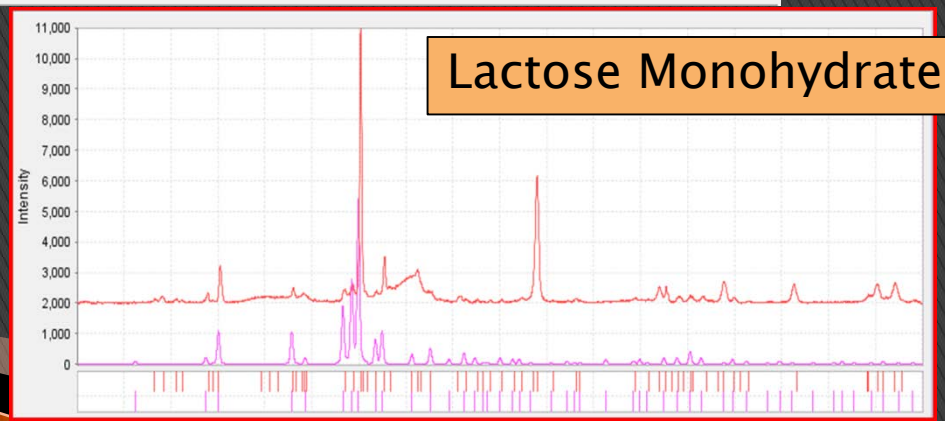
This process is repeated for cellulose Iβ and alpha lactose monohydrate. The cellulose Iβ has a nano crystallite size. In these examples we offset the simulation and experimental data to show the phase contribution to the experimental pattern The offset is a user selectable choice.

Cellulose I β, 65 Å

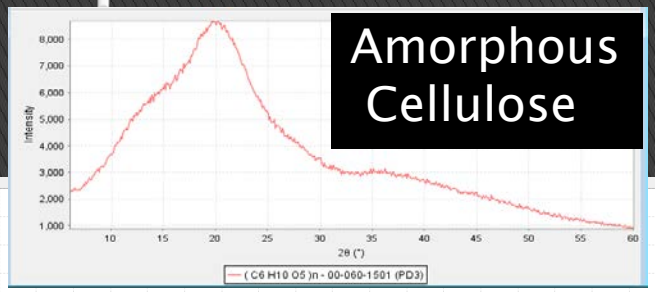




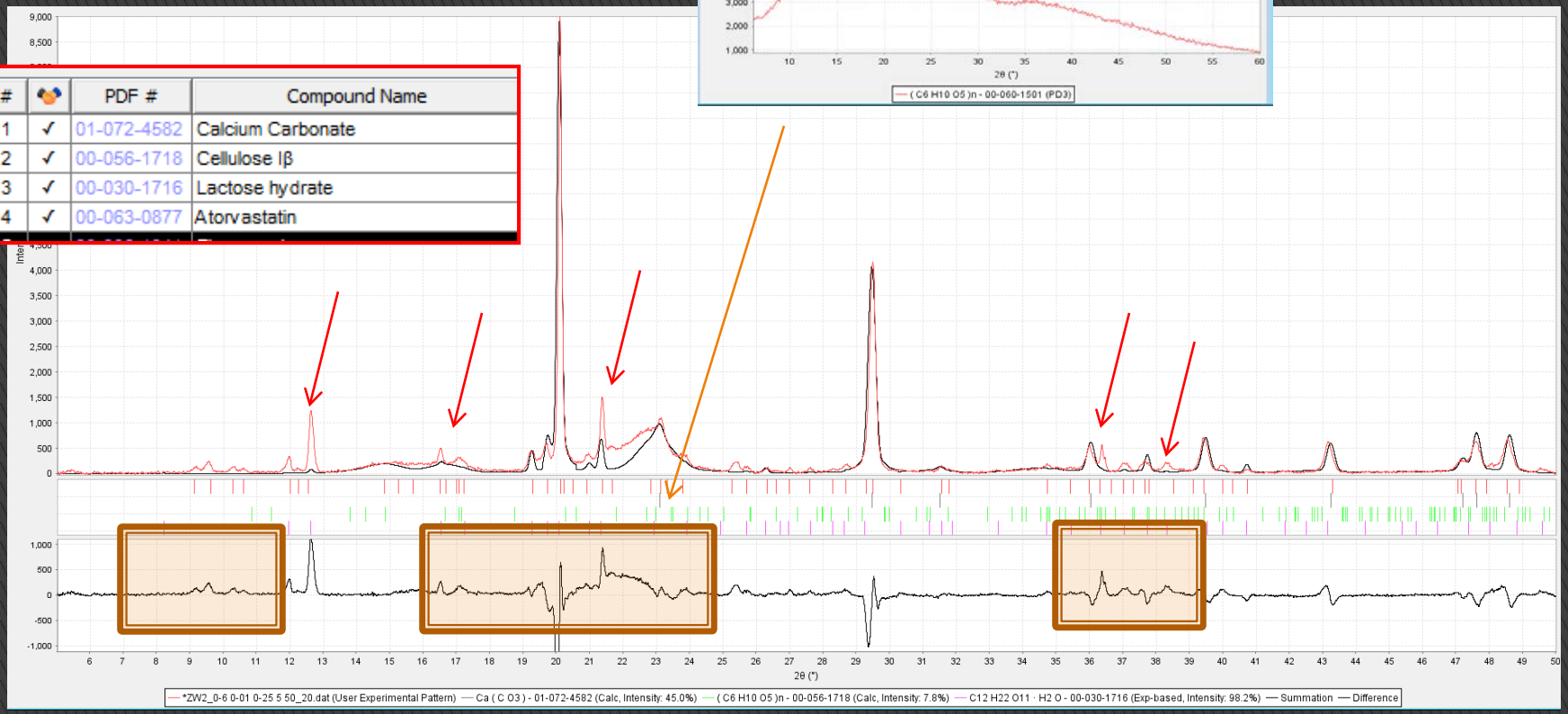
Lactose Monohydrate, 550 Å



Summation – 3 phases



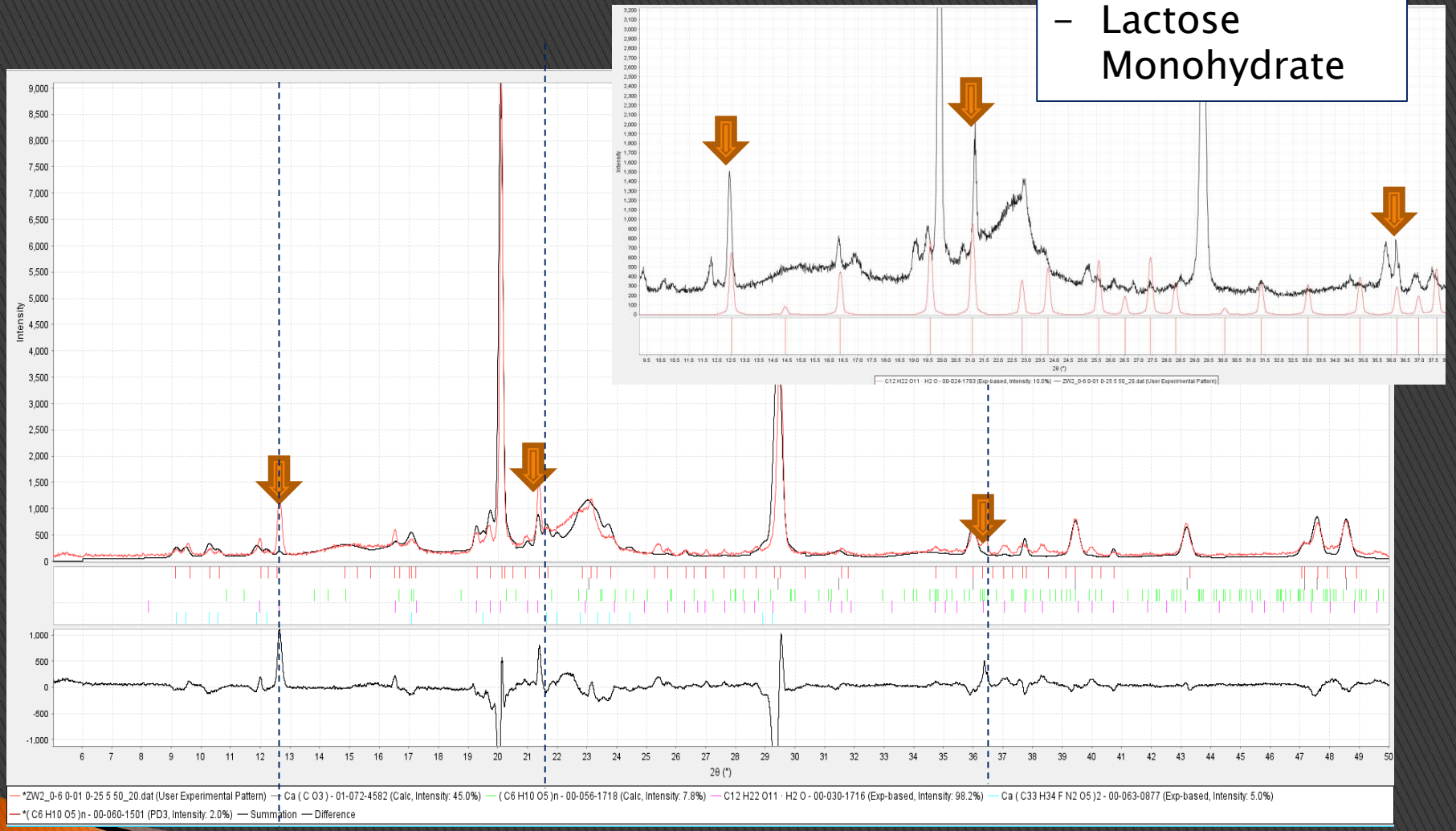
#		PDF #	Compound Name
1	✓	01-072-4582	Calcium Carbonate
2	✓	00-056-1718	Cellulose Iβ
3	✓	00-030-1716	Lactose hydrate
4	✓	00-063-0877	Atorvastatin



We can now sum all three contributions from calcite, alpha lactose monohydrate and cellulose Iβ. This produces the combined simulation, shown in black, directly under the experimental data in red. The graphic below these data is the difference plot. Close examination of the difference plot reveals 3 areas of interest which are in the highlighted boxes. In the box on the far left are residual peaks that can now be identified as the API, atorvastatin. The broad feature in the middle box corresponds to amorphous cellulose. The residual peaks in the third box and with the arrows, correspond to lactose monohydrate.

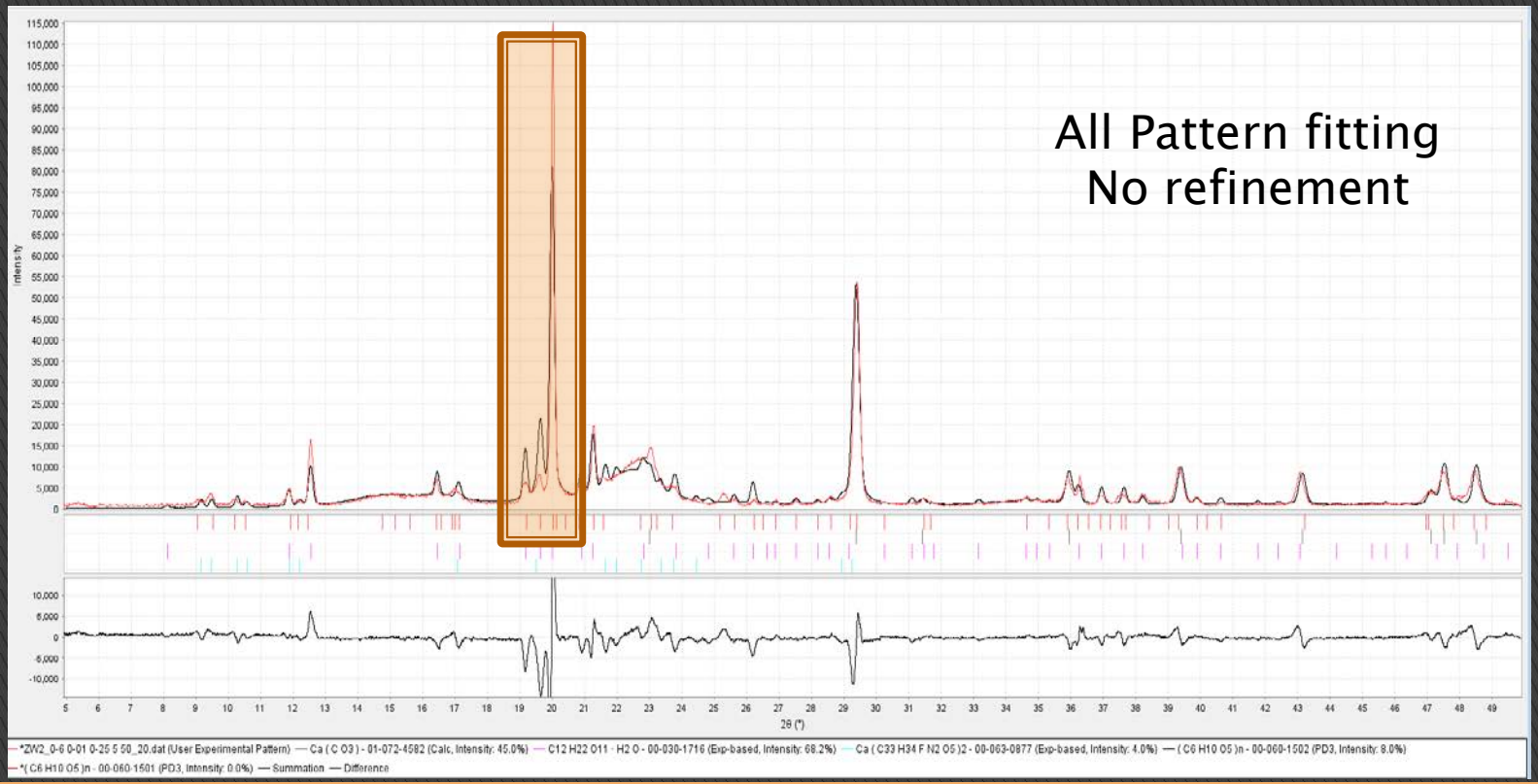
Summation – 5 phases

- Lactose Monohydrate



The summed simulation shows that we are now close to a final answer but still have residual peaks that appear to be due to a second reference for lactose monohydrate, as shown in the top right insert.

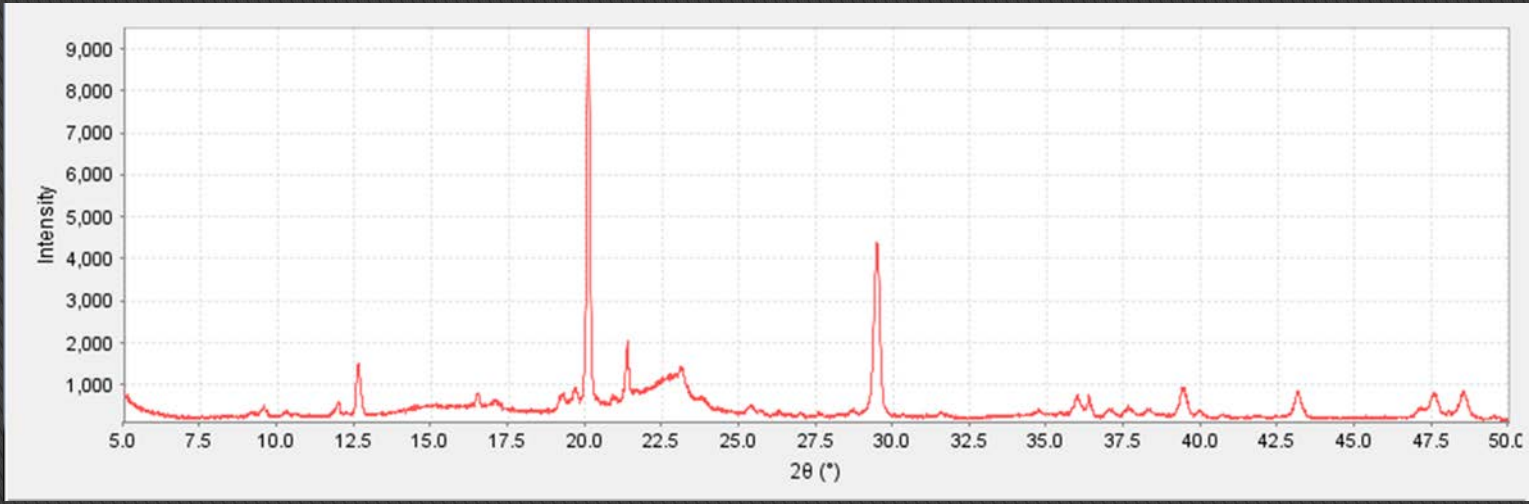
Final Fit – Orientation of Lactose Monohydrate



We believe that it is unlikely that there are two forms of lactose monohydrate in this sample and it may be possible that there is a single phase, but it is highly oriented, causing residual peaks when compared to a randomly oriented reference. The simulation software contains a March-Dollase one direction orientation function. Applying the function along the (011) lattice plane results in all peaks matching a single phase, but there is still some intensity mismatch as shown in the box. We suspect that a higher order orientation function would resolve the small residual. Lactose monohydrate has a platelet morphology and easily orients.

Lipitor®

1	✓	01-072-4582	Calcium Carbonate	0.610	36.87	3.23*	
2	✓	00-056-1718	Cellulose Iβ	0.078	4.715	8.27	
3	✓	00-030-1716	Lactose hydrate	0.682	41.222	1.55	
4	✓	00-063-0877	Atorvastatin	0.187	11.303		



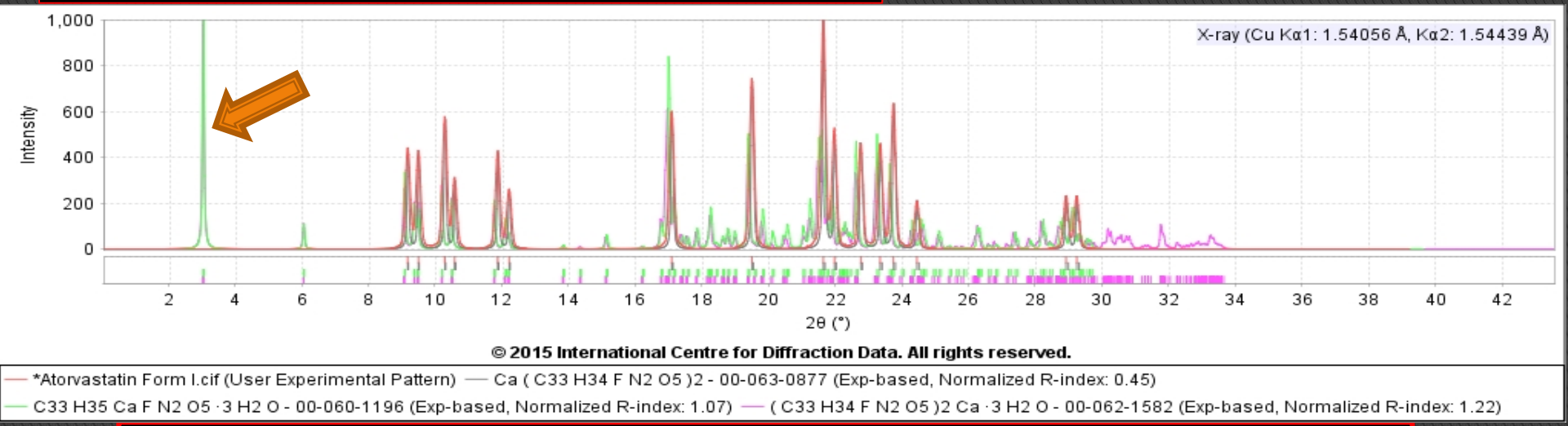
			Int %
01-072-4582	Calcite		35
00-056-1718	Cellulose Iβ - 65Å	Alternative	6
00-060-1501	Amorphous Cellulose	00-062-1502 Microcrystalline Cellulose (contains amorphous content)	2
00-030-1716	Lactose Monohydrate (oriented 011)		54
00-063-0877	Ca Atorvastatin *USP 5,969,156* *Form I*		3

The final solution by pattern fitting identified five phases including an amorphous cellulose and nanocrystalline cellulose. The simulation also simulates the crystallite size of each phase and provides a series of relative intensities. If desired, the relative intensities could be used in a RIR calculation for phase quantitation. The two additional phases added to the preliminary phase identification, including the API, are present in low concentration.

What is - Ca Atorvastatin *USP 5,969,156 Form I ?*

24 Determinations, many polymorphs and hydrates – 0, 1.0,1.5 and 3

Ca Atorvastatin Trihydrate Normalized R-Index



Patent PDF 00-063-877 matches Martin Vickers
data from University CollegeLondon Ca Atorvastatin *Trihydrate*
PDF-00-060-1196
and
PDF-00-062-1582 "Synchrotron X-ray powder diffraction data of atorvastatin." Antonio, S., Benini, F., Ferreira, F., Rosa, P., Paiva-Santos, C. Powder Diffr. 23, 350 (2008).

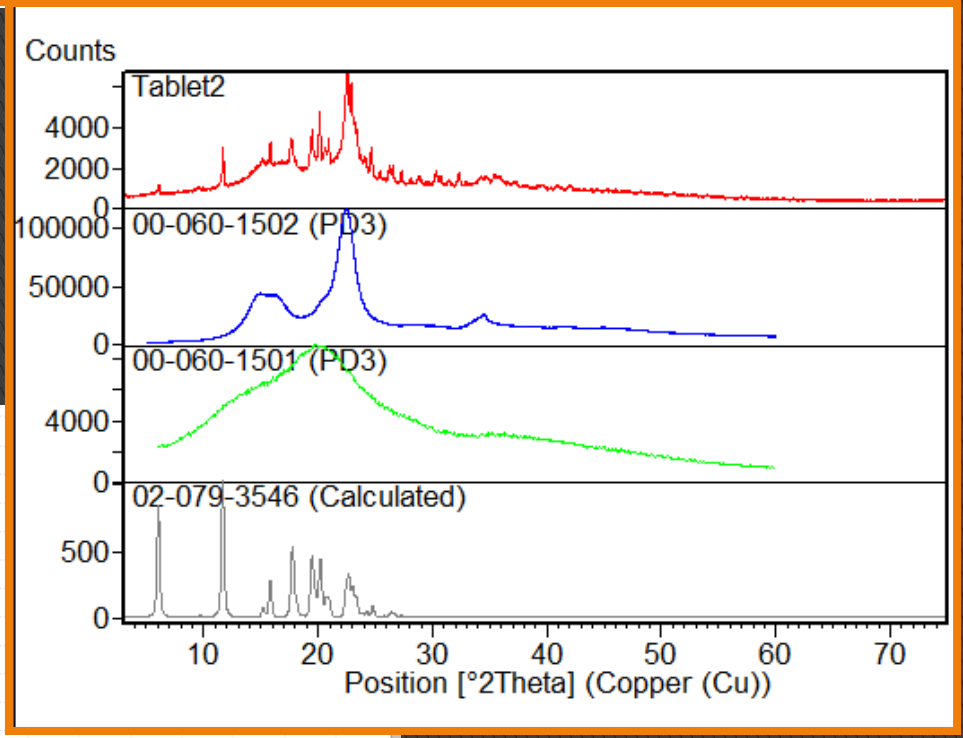
The original phase identification identified the API as atorvastatin and referenced *United States Patent 5,969,156.*
The PDF-4/Organics database contains 24 determinations of atorvastatin and its hydrates. We used a normalized R-Index similarity index (a cluster program) that is embedded with the database to match USP 5,969,156 to other atorvastatin references and can clearly identify the patent Form I phase as calcium atorvastatin trihydrate. The matching references are cited above. The graph shows a comparison of the 3 references. The data also shows that there is a major peak at 3 degrees 2θ, that is missed in most experimental data scans *and the patent data*.

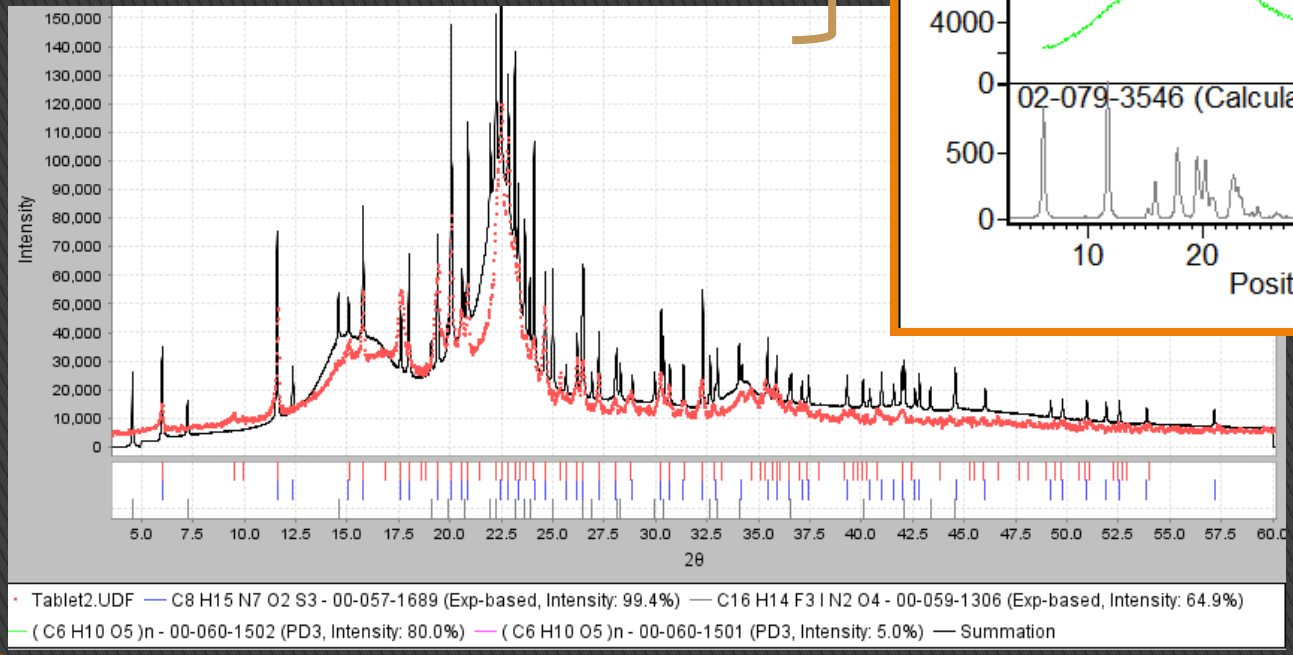
Full Pattern Analysis

Example 2 – PEPCID AC®

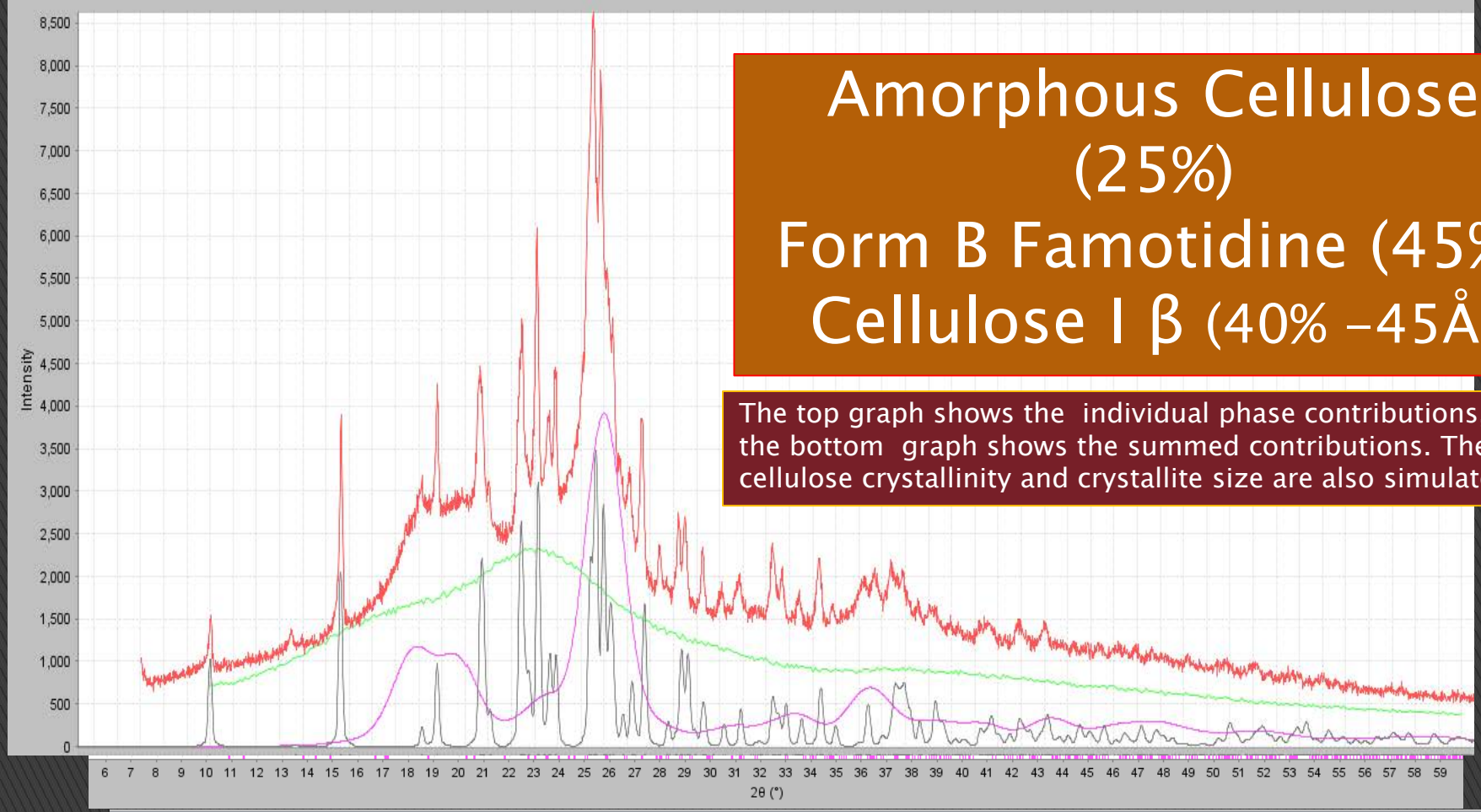
Phase Identication and Pattern Fitting – PEPCID AC®

Calculated pattern
Experimental amorphous pattern
Experimental nano pattern





Similar to case 1, a preliminary phase identification (not shown) quickly identified cellulose Iβ and famotidine the API. Note, you have to be careful because some search programs will treat the broad nanomaterial peaks of cellulose Iβ as background and not find this phase. Analysis of the residual pattern reveals the presence of amorphous cellulose (PDF 00-060-1501). The combined pattern simulation, in black, for the three phase solution can be compared to the experimental data in red. All major features are accounted for.



Amorphous Cellulose (25%)
Form B Famotidine (45%)
Cellulose I β (40% –45Å)

The top graph shows the individual phase contributions, the bottom graph shows the summed contributions. The cellulose crystallinity and crystallite size are also simulated.

Experimental versus Summed Components

Full Pattern Analysis

Example 3 – Zirconium Oxide

In this example, using an inorganic oxide, we demonstrate factors that influence the editorial classification of materials as amorphous or nanocrystalline references.

These data, kindly provided by the Eastman Kodak company were produced in a Parr reactor that varied temperatures and pressure in a deliberate attempt to produce controlled size nano particles. The method of preparation, XRD data, and other complimentary analytical analyses all contributed to the determinations by ICDD editors of amorphous and/or nanocrystalline designations for these references.

Method of Preparation

Amorphous Reference

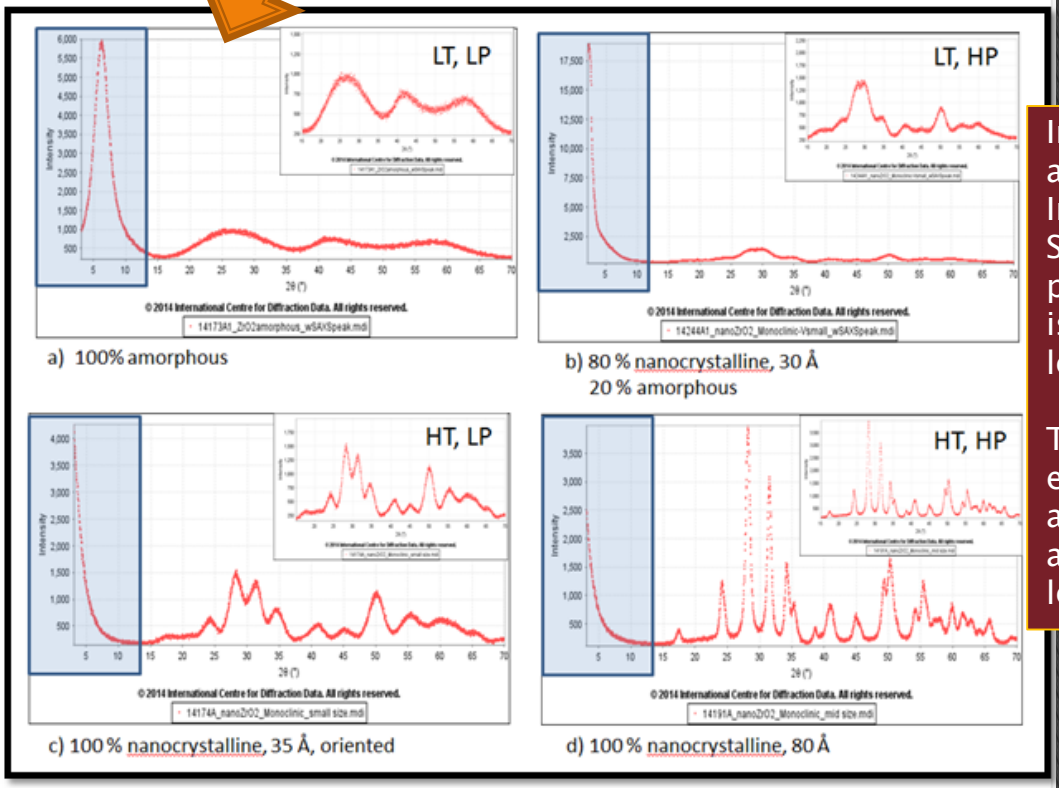


Figure 6. X-ray diffraction patterns for a series of ZrO_2 nanomaterials synthesized in a Parr reactor with varying temperature and pressure. (a) low temperature, low pressure, (b) low temperature, high pressure, (c) high temperature, low pressure, (d) high temperature, high pressure.

In these experiments temperature and pressures were systematically controlled. In the blue box, we highlight the low angle SAX data which are due to the nano crystalline particles. In the top 2 data sets the SAX peak is clearly visible and corresponds to 19 Å (top left) and 36 Å (top right).

The bottom two data sets can be completely explained using a ZrO_2 reference and applying a nano crystallite size of 80 Å (bottom right) and 35 Å and an orientation function (bottom left).

Complimentary Data

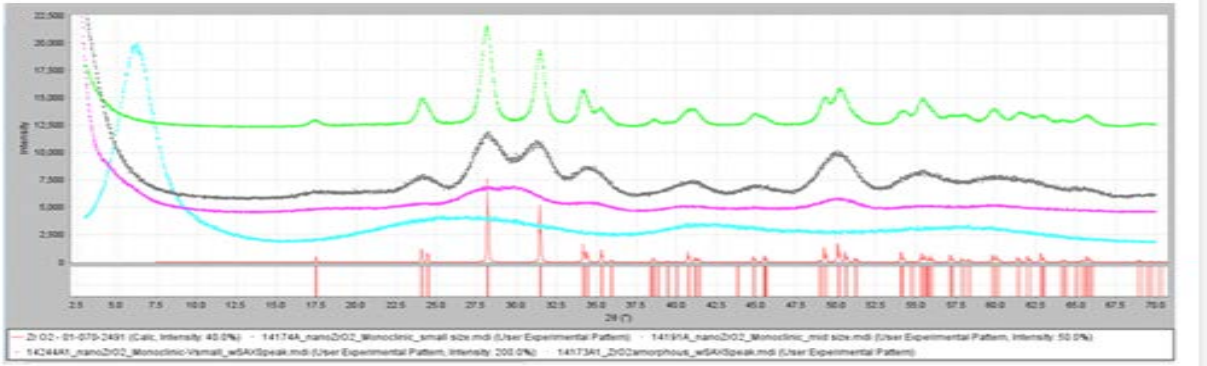
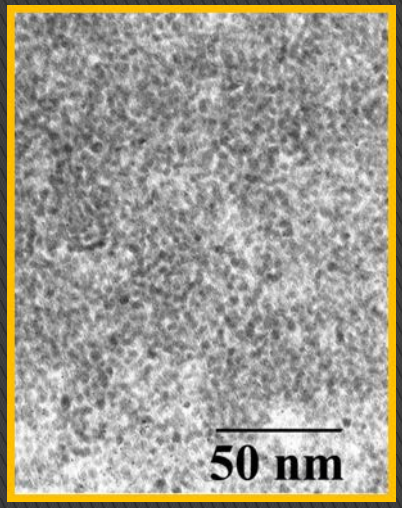


Figure 7. The X-ray diffraction patterns of a series of nano-sized zirconia's showing how the X-ray diffraction patterns change as crystallite size is reduced. The bottom pattern is the highly crystalline reference pattern PDF 01-070-2491. The experimental diffraction data are identical to Figure 6.



These are the same data from the previous slide now shown on a single display that also includes the crystalline reference pattern, which are the sharp peaks on the bottom of the graph. A TEM photograph of the nanoparticles are shown on the far right.

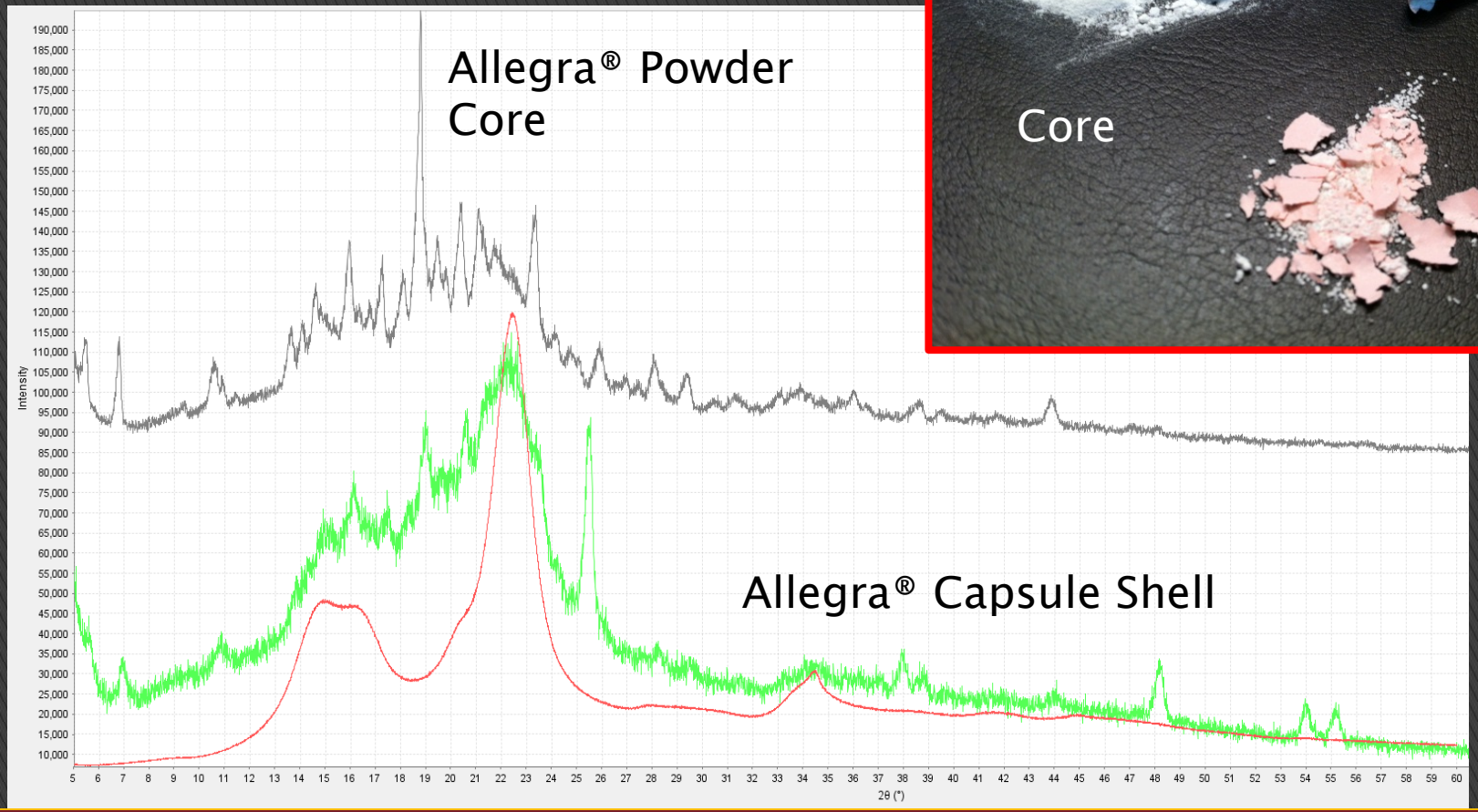
As mentioned in the earlier slide we can completely explain the top two data sets, in green and in black, using a nano crystallite simulation of the reference data of 80 Å and 35 Å respectively. We now focus on the blue curve that has a SAX peak (particle size) at 19 Å. You can see that the intensity distribution in blue, does not align with the reference or the other data sets. The peak maximum is shifted, an indication but not definitive proof, of the amorphous state. No matter what crystallite size we attempt to simulate we cannot match the scattering profile shown in the blue data set – as a result of these combined factors we designate this data as the amorphous reference.

Once we define the amorphous reference we can now interpret the pink data set as 80% crystalline, 30 Å nano ZrO_2 with 20% amorphous contribution.

Full Pattern Analysis

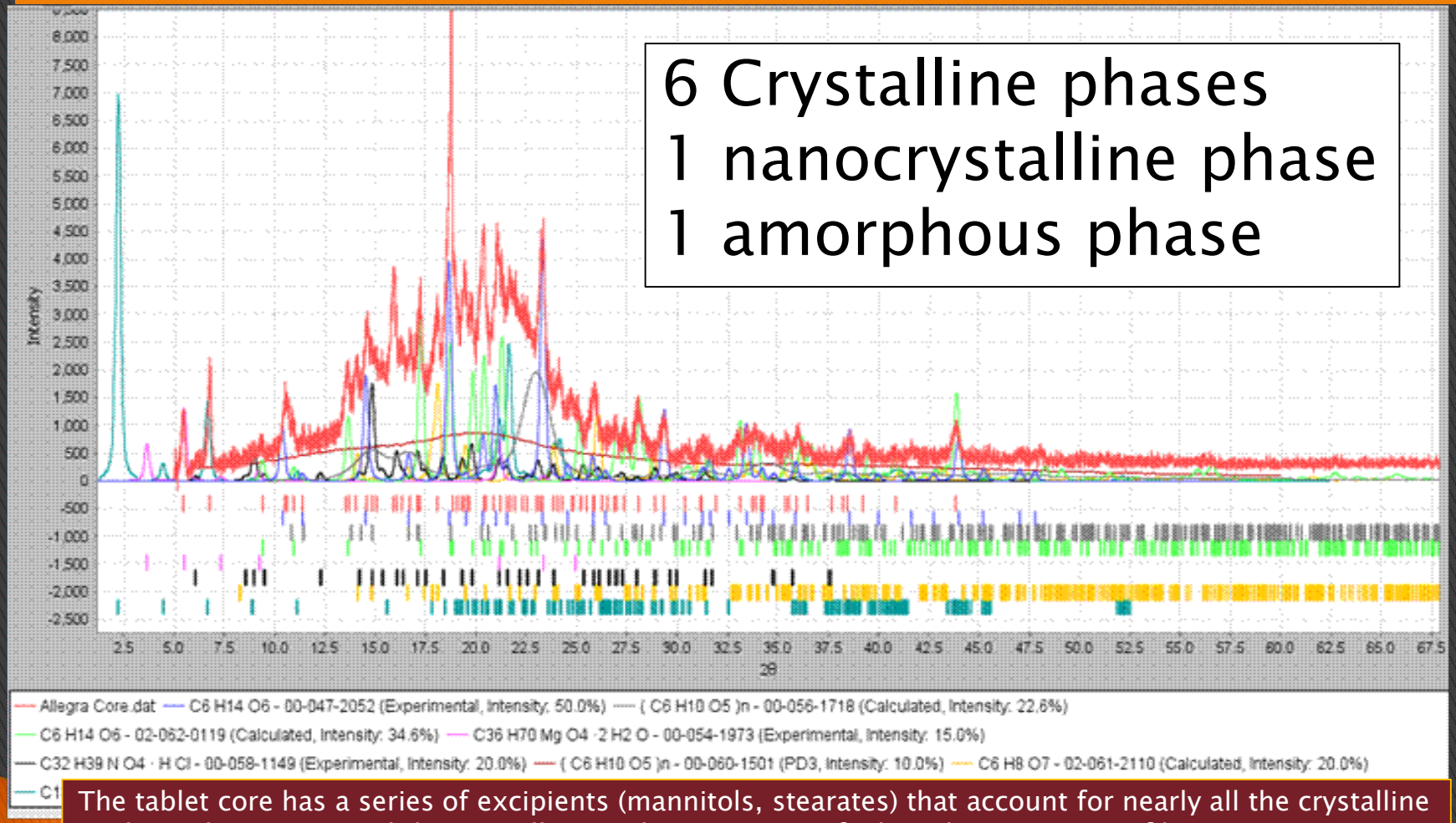
Example 4 – Allegra®

Allegra®



Allegra is a marvelously complex formulation that we have studied several times over the past few year. The data sets shown here are all from ground Allegra tablets but taken at different times by different researchers. When first grinding an Allegra tablet it becomes immediately apparent that the tablet has an architecture consisting of a hard shell with a soft core. The soft core also has different size particles including fines – as shown in the picture on the top right. If you dissolve the pill in water the residual cellulose fibers are easily seen. In the above data, it is clear that the shell contained cellulose and TiO2 pigment among its ingredients.

8 phase Pharmacuetical Tablet – Allegra®, Uses all Tools

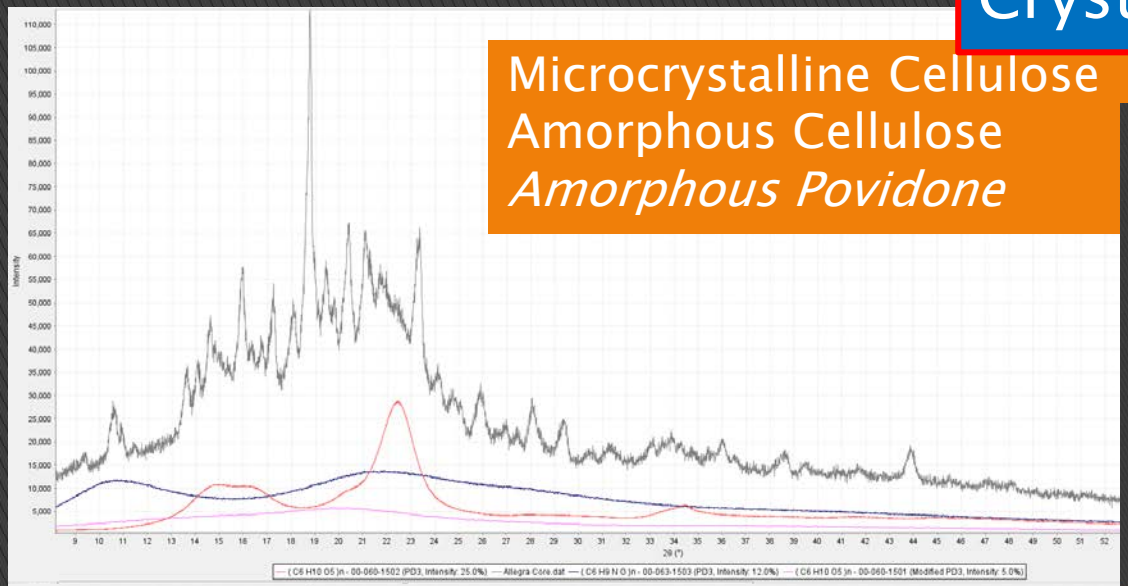


The tablet core has a series of excipients (mannitols, stearates) that account for nearly all the crystalline peaks in the pattern and the crystalline peaks are on top of a broad scattering profile containing amorphous and nanocrystalline ingredients. The experimental data are shown in red and all the individual contributing ingredients are shown underneath.

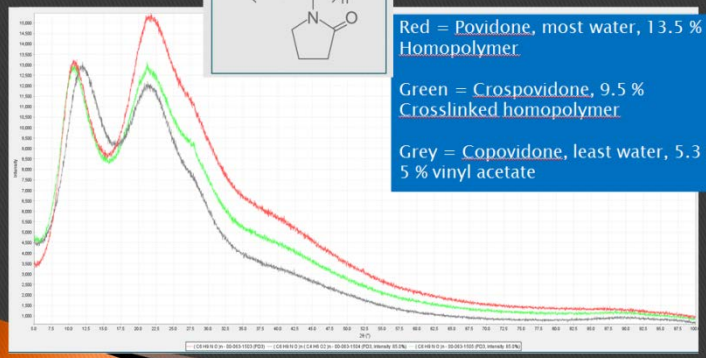
Allegra® Core

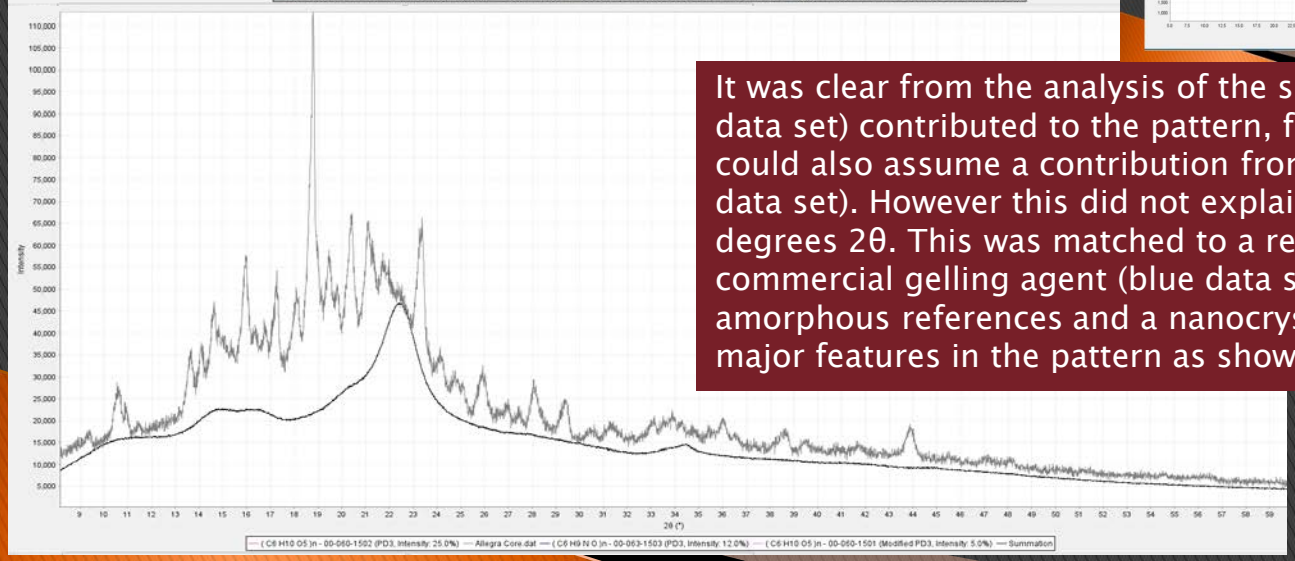
Material Identification Using Amorphous and Nano Crystalline references

Microcrystalline Cellulose
Amorphous Cellulose
Amorphous Povidone



Povidone Hydration





It was clear from the analysis of the shell data set that cellulose (red data set) contributed to the pattern, from the sloping baselines we could also assume a contribution from amorphous cellulose (pink data set). However this did not explain the intensity seen below 14 degrees 2θ. This was matched to a reference of povidone, a commercial gelling agent (blue data set). The combined data of 2 amorphous references and a nanocrystalline reference explains the major features in the pattern as shown in the bottom figure.

Allegra®

Effect of Water Vapor Sorption on Local Structure of Poly(vinylpyrrolidone)

JING TENG, SIMON BATES, DAVID A. ENGERS, KEVIN LEACH, PAUL SCHIELDS, YONGLAI YANG

SSCI, a Division of Aptuit, 3065 Kent Avenue, West Lafayette, Indiana 47906

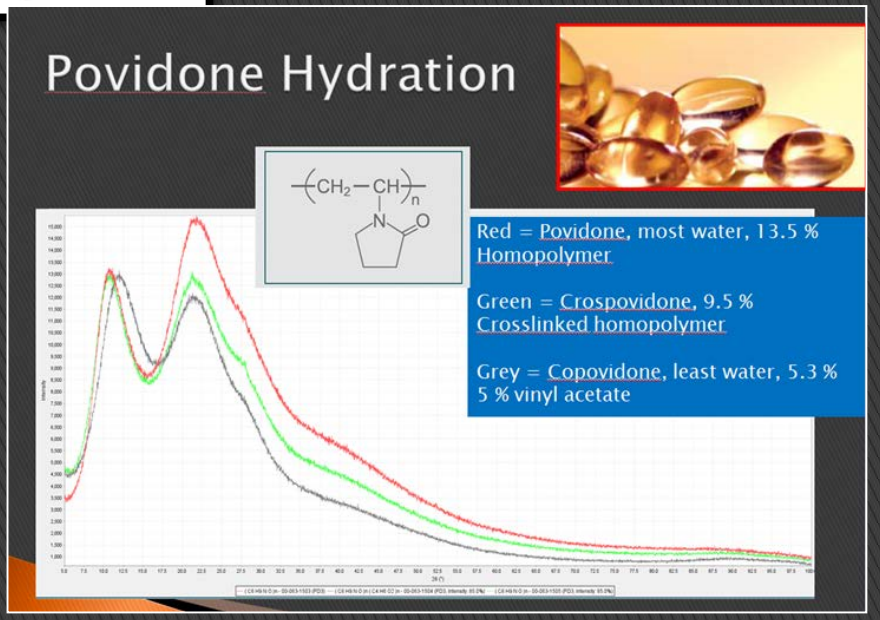
Received 29 January 2010; revised 5 April 2010; accepted 5 April 2010

Published online 25 May 2010 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22204

Reference data for Poly vinylpyrrolidone polymers and the common excipients – povidone, crospovidone and copovidone were obtained by using USP references and grant work by Roman Shpanchenko, formerly at Moscow State University, and now at Samsung SDI company. Roman collected the patterns but also measured water content of these gelling agents by TGA/DSC.

Nearly simultaneously, an important research publication on poly vinylpyrrolidone was produced by the research team at SSCI (reference above) that provided detailed structural interpretations of the data and related physical properties.

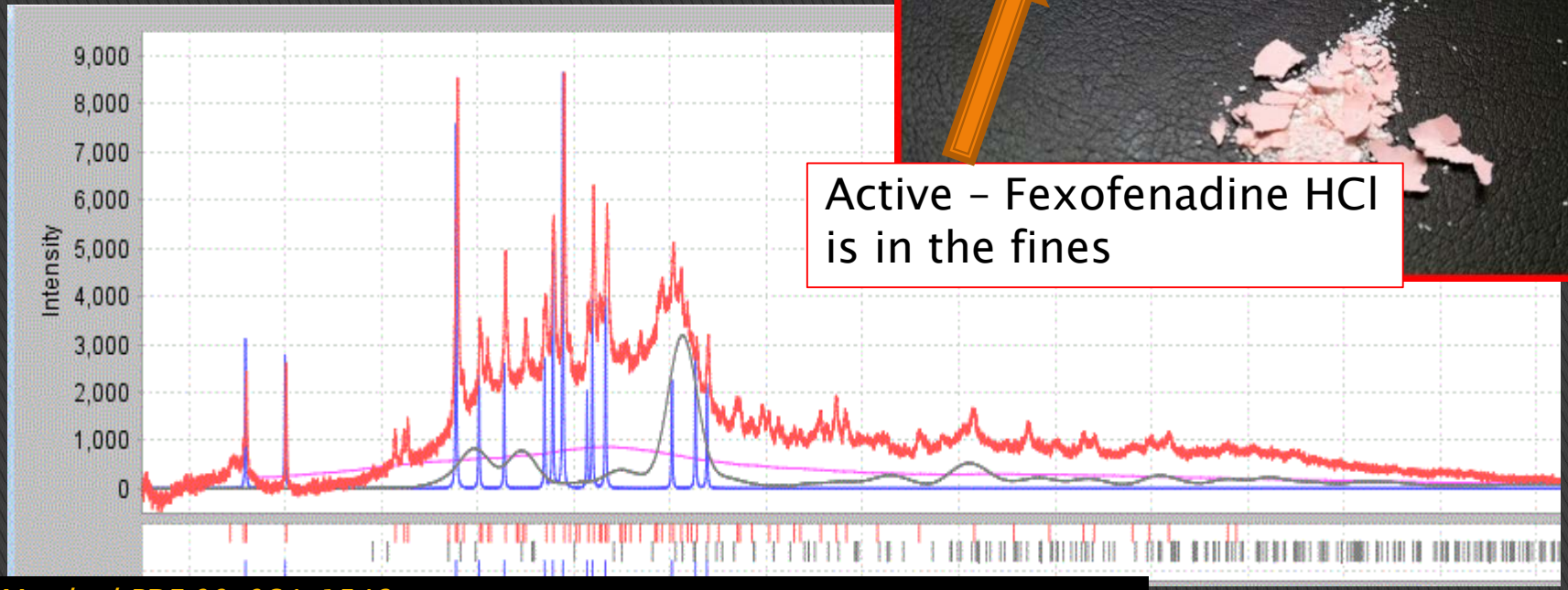
The diffraction data, supporting TGA/DSC data, and cross referenced SSCI publication can all be found as part of the reference entries for these three excipients in PDF-4/Organics



Allegra
– Synchrotron Data

Argonne National Light Source
Thanks to Kai Zhong, Jim Kaduk

Active – Fexofenadine HCl is in the fines



Matched PDF 00-064-1548
"Fexofenadine hydrochloride." Kumar, L., Shahnwaj Alam, Md., Lal Meena, C., Jain, R., Bansal, A. Profiles Drug Subst., Excipients, Relat. Methodol. 34, 153 (2009). – unfortunately cut data off at 30 degrees

Not PDF 00-058-1149- "Fexofenadine polymorphs and processes of preparing the same." Rao, D., Kankan, R., Gangrade, M., Birari, D., WO 019175 A1. PCT Int. Appl. (2005).

2 Polymorphs and 2 solvates

In 2015, the ICDD had a core sample measured in a capillary at the Argonne Advanced Photon source. Apparently the capillary preparation concentrated the fines and for the first time we clearly observe the API, fexofenadine hydrochloride. The pattern matches PDF 00-064-1548, not the patent reference (citations above).

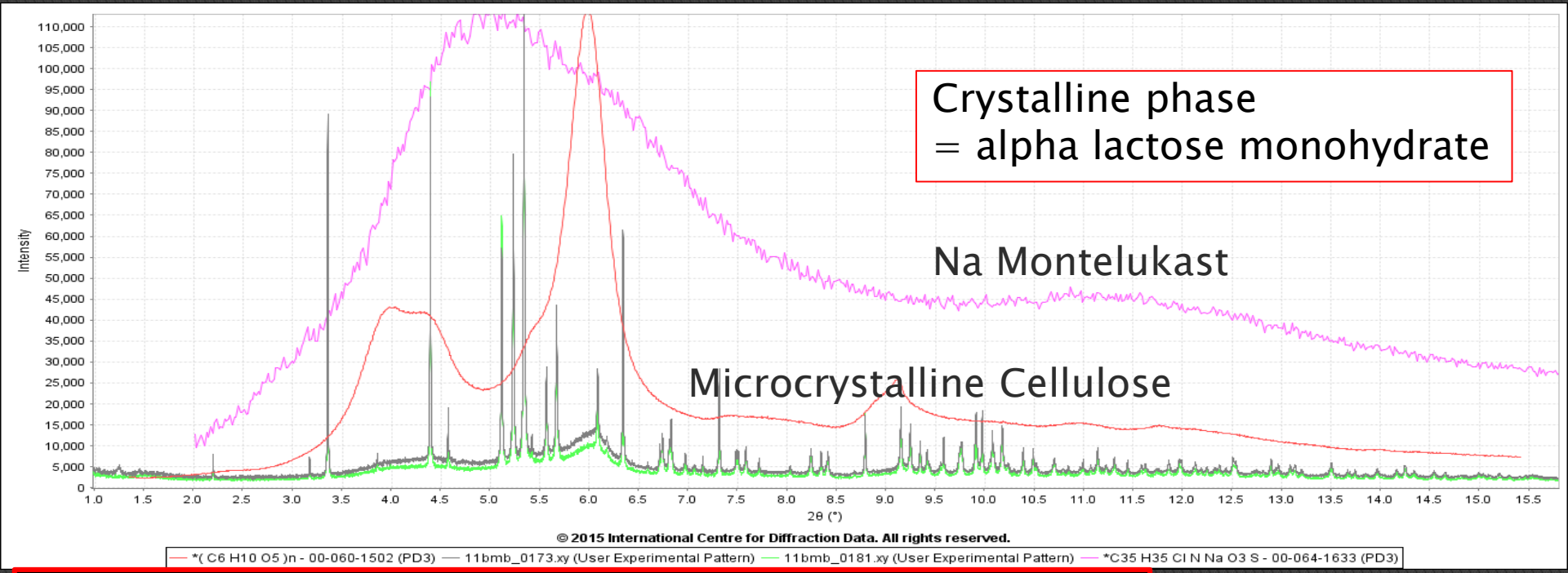
Full Pattern Analysis

Example 5 – Singular®

The analysis of Singular® was inspired by two events. The first being a presentation by Simon Bates in PPXRD12 demonstrating that small amounts of absorbed water could be measured by analyzing its scattering pattern and using synchrotron data. The second event was the measurement of a Sodium Montelukast amorphous reference pattern that was published by the ICDD in 2014.

This experiment was designed to determine the presence and relative amount of an amorphous API, sodium Montelukast, in a formulated product. Laboratory data taken in 2014 on a Singular® tablet, indicated the presence of Na Montelukast, but was not definitive, predominately due to the experimental design. This following standard addition experiment was performed at the Argonne Advanced Photon Source.

Singular®



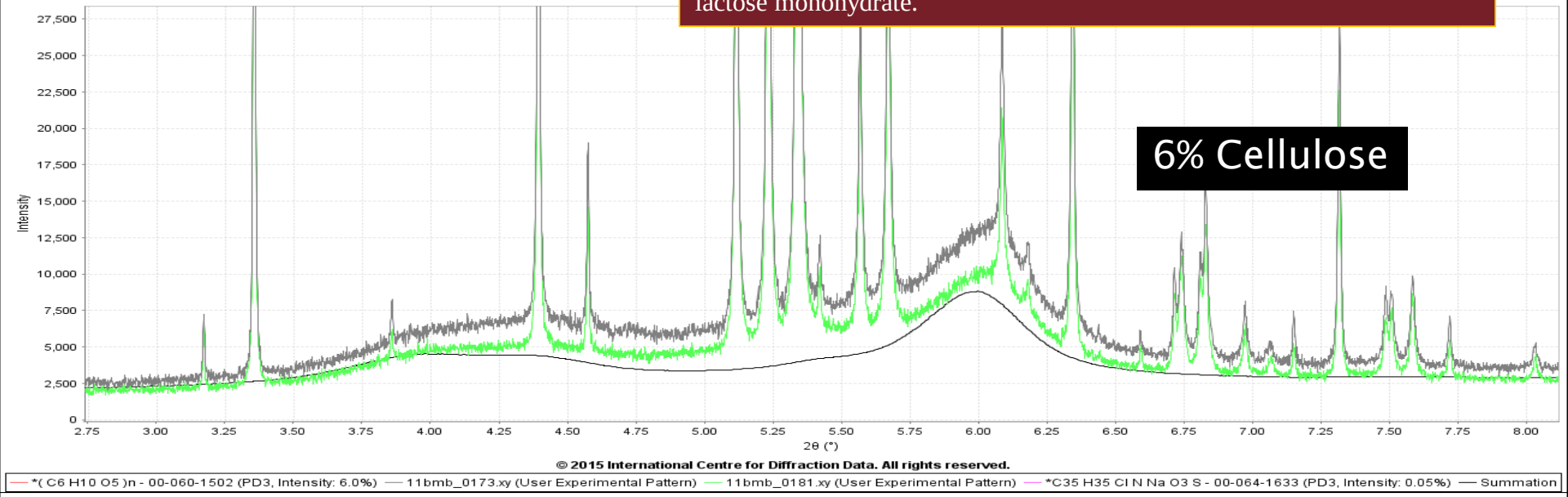
Singular (green data set)
Singular plus 5% Na Montelukast (black data set)

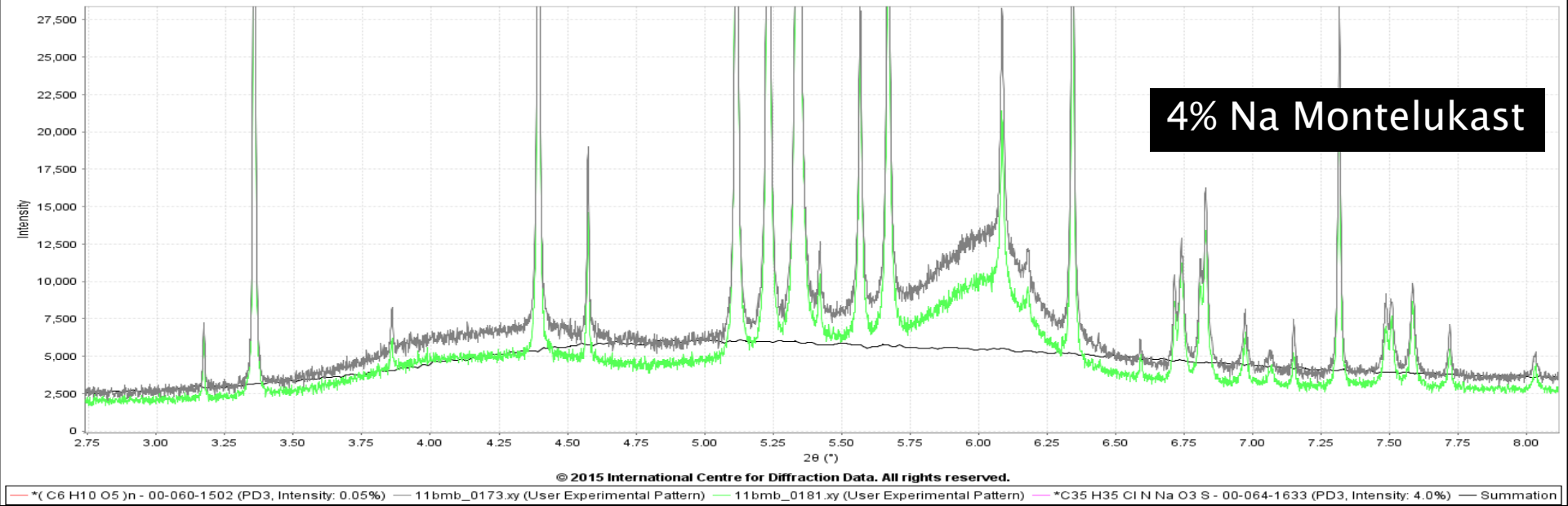
Two capillaries were packed with a ground tablet of Singular®. The second preparation used a 5% by weight addition of sodium Montelukast that was blended into the ground Singular® tablet. Conventional phase identification identifies alpha lactose monohydrate and microcrystalline cellulose. We then use pattern fitting and summation to try to determine the sodium Montelukast content in each data set.

Some of the reference data were collected on a synchrotron and other reference data collected with conventional laboratory Cu radiation, our software program can convert between different wavelengths. Most of the graphs show the synchrotron radiation at 0.41332Å.

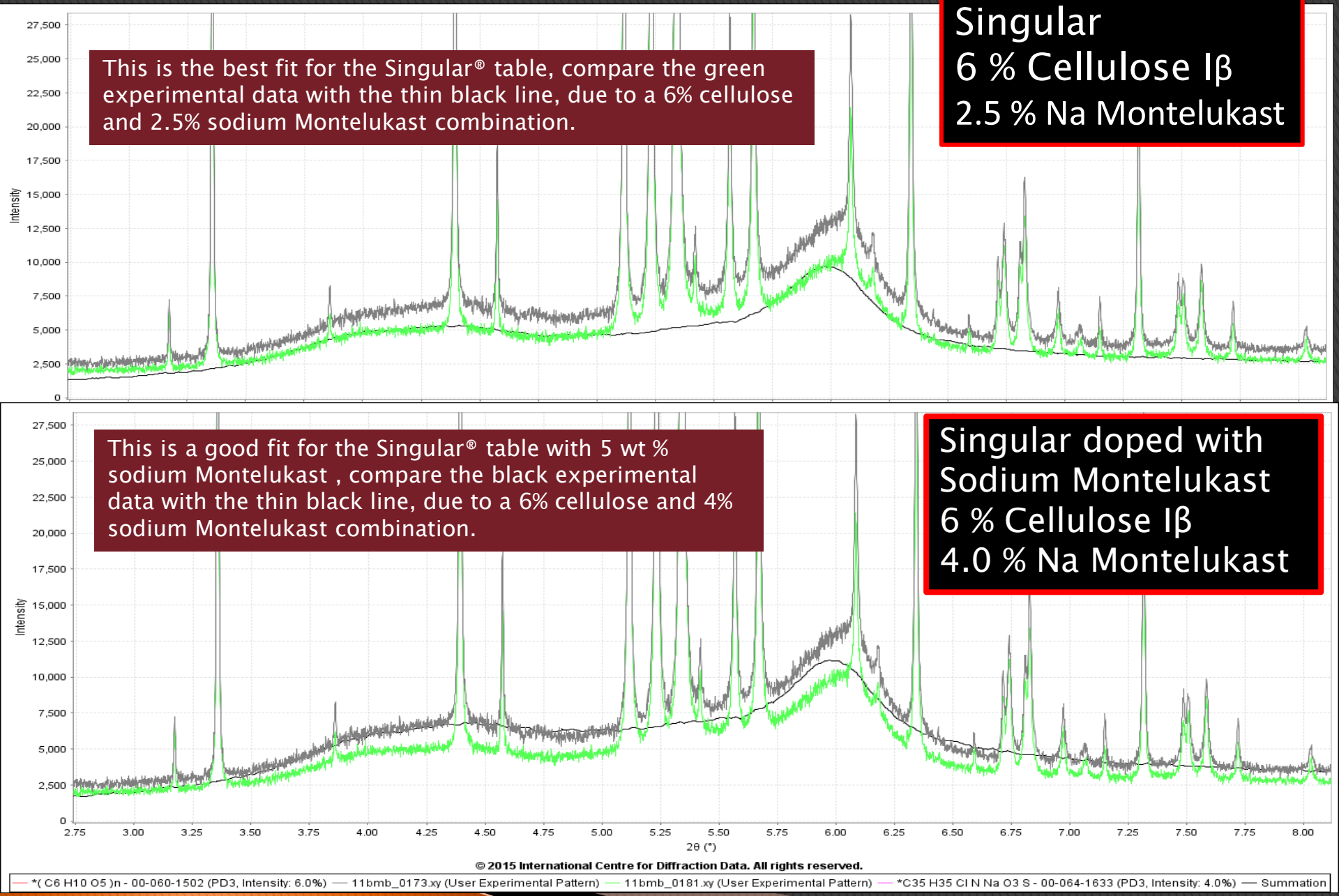
Singular® Fit

These data are shown to demonstrate that neither cellulose nor sodium Montelukast alone, can completely explain the observed diffraction patterns. The summations are shown in the thin black lines underneath the two experimental data sets. All crystalline peaks are alpha lactose monohydrate.

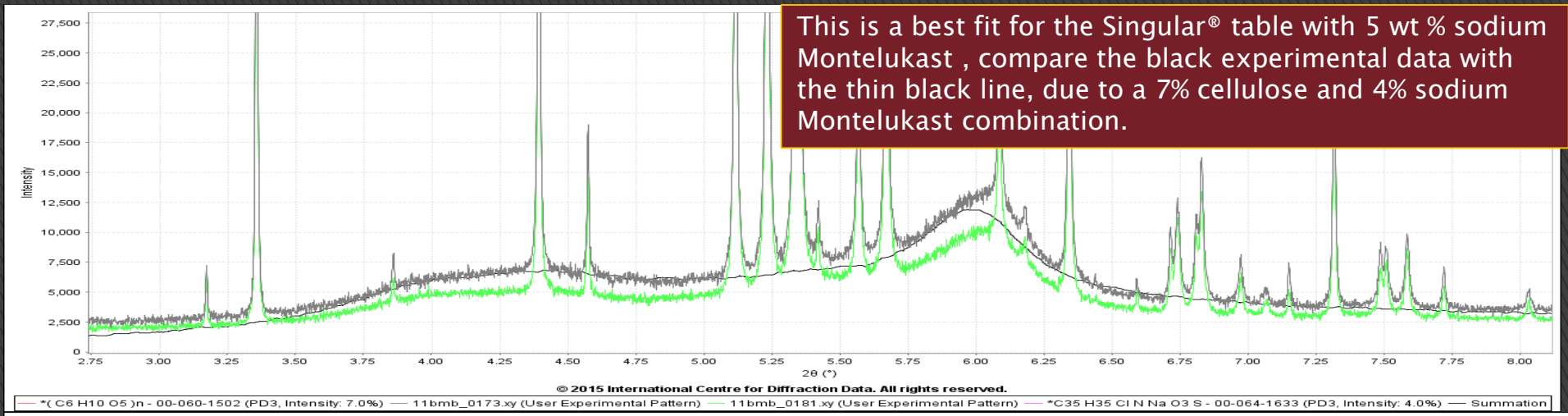




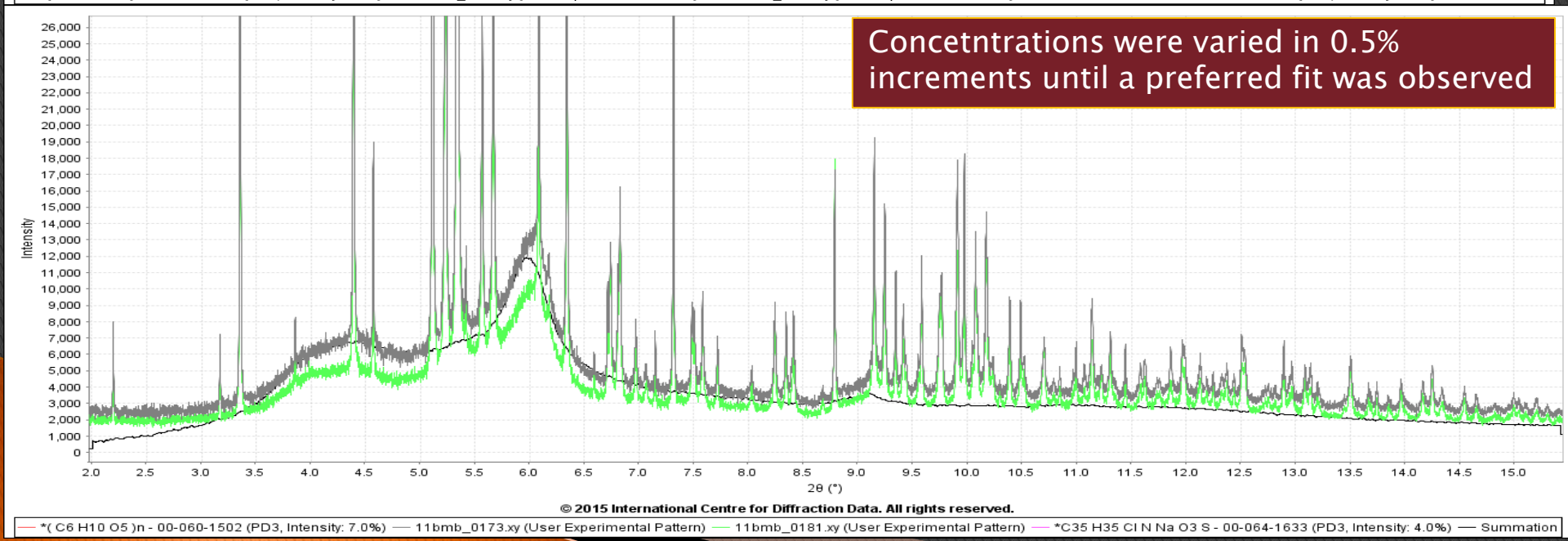
Singular® Fit 1



Singular® – 7% cellulose Iβ mix with 4 % Montelukast



This is a best fit for the Singular® table with 5 wt % sodium Montelukast , compare the black experimental data with the thin black line, due to a 7% cellulose and 4% sodium Montelukast combination.



Concetntrations were varied in 0.5% increments until a preferred fit was observed

Singular® Full Pattern Analysis

Singular has 10.4 mg Na Montelukast per tablet of 200mg. The original has 5 wt % and doped ground tablet should have ~ 10 wt %

We found 2.5 and 4.0% based on a peak height intensity.
To quantify one would need a scaling factor (RIR). If we scaled based on the single standard addition experiment it would estimate that the original tablet contained 6% Na Montelukast.

Conclusion: Careful experiments and good reference patterns can be used to detect small concentrations of amorphous materials.

We estimate that we could visually determine changes in ~1 wt. % amorphous content by pattern fitting methods using these data sets.
Other authors have shown detection limits of ~0.1 wt. % amorphous content using multipoint standard addition methods and optimized counting statistics with synchrotron radiation.

Examples –

Having both amorphous and nanocrystalline contributions

- Lipitor
- Pepcid AC
- ZrO_2
- Allegra
- Singular

All examples shown contained both nanocrystalline and amorphous materials in the same data sets.

Simple in concept, difficult in execution

Simple for the user

- Visual
- Additive patterns from the PDF database
- Easy to use

The ability to detect amorphous and nanomaterials by Powder diffraction whole pattern methods required a multi-year software development effort and new editorial procedures and policies for these materials. It required a full library of graphical plotting methods so that the user could analyze common specimen effects (crystallite size, orientation), various wavelengths and various detector systems.

Difficult for the ICDD

Crystalline

- All patterns digital
- Orientation Function
- Develop crystallite size function

Amorphous

- Define amorphous materials
- Collect experimental digital patterns for amorphous materials
- Develop similarity index

Both

- Background correction
- Modifications for various wavelengths
- Modification for neutrons, electrons, X-rays
- ID or 2D detector systems

Criteria for amorphous references

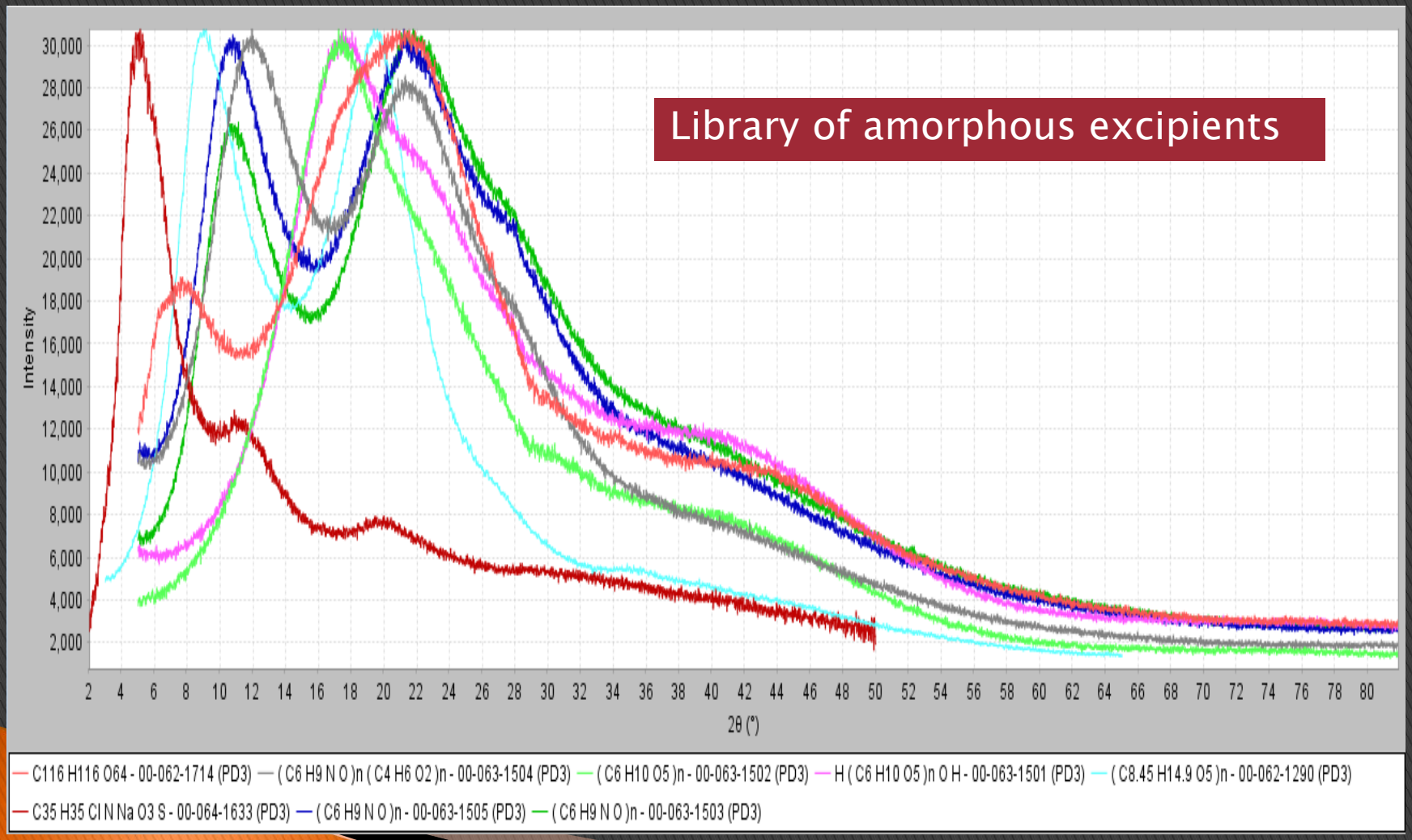
- Chemically purity – verified
- Chemically stable
- Cannot be modeled or simulated as a crystalline material
- Method of preparation
- Confirming analytical support data (DSC, TGA, NMR, microscopy, SEM, TEM)

What is nanocrystalline and what is amorphous has been argued by numerous diffraction experts in court cases spanning decades. The ICDD uses a series of criteria and supporting analytical data to make these determinations. No single criteria, such as those listed above, is definitive by itself. The ICDD quality and review system is based on using combinations of criteria.

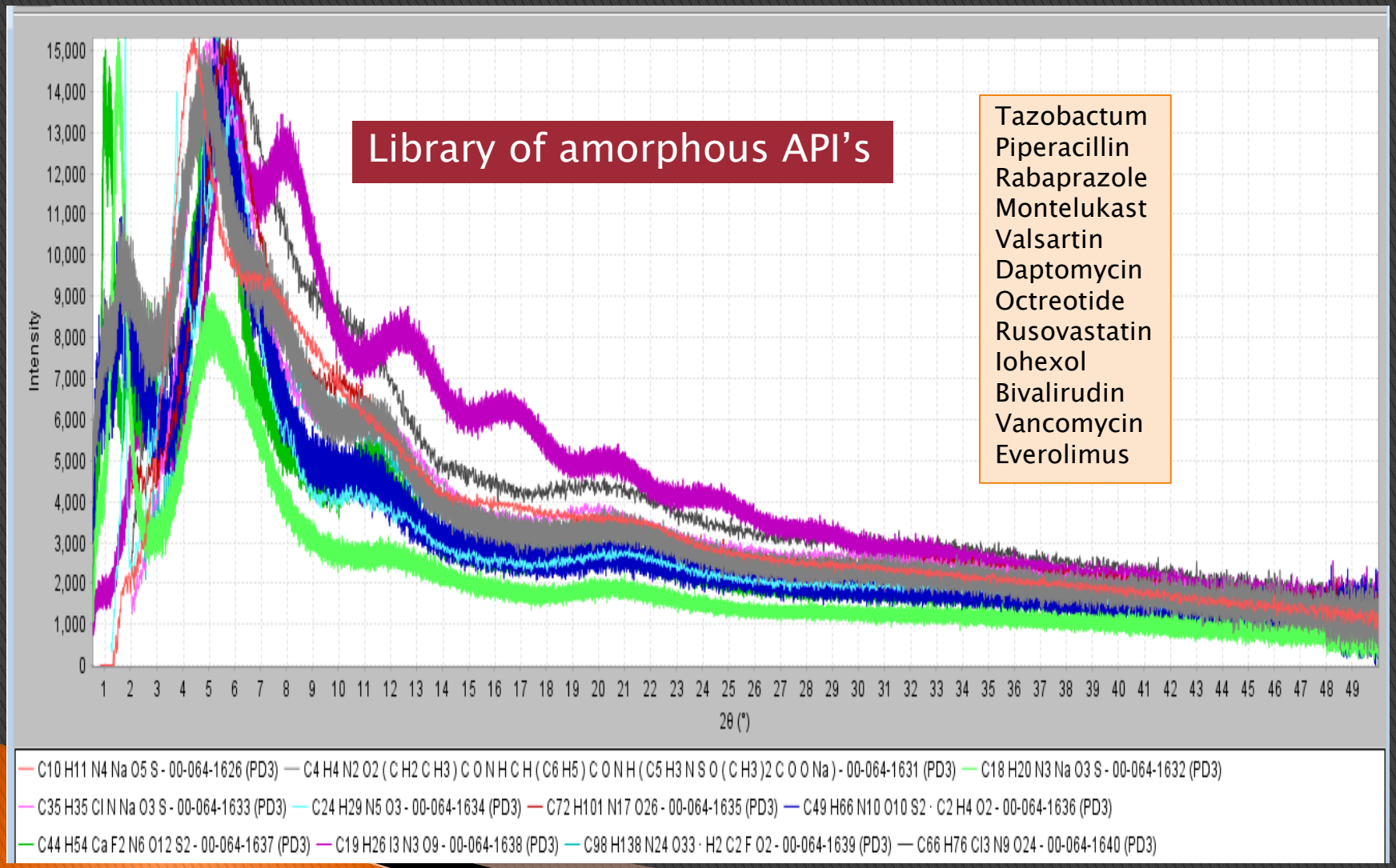
THE DEVELOPMENT OF NANOMATERIALS AND AMORPHOUS REFERENCES

Material	Supporting Data
Nano Microcrystalline Cellulose	TGA/DSC, Pair Dist. Function, Multiple samples, C, H, N analyses, SEM analysis
Nano Apatite	TEM analyses
Substituted celluloses (Methyl, Acetate)	NMR degree of substitution, Pair Dist. Function Multiple samples under varying process conditions
Amorphous Cellulose	High purity standards, 3 cryogrinding studies
N-vinyl-2-pyrrolidone (Povidone)	C, H, N analyses, TGA/DSC, USP references
Polystyrenes, Polyethylene, Polypropylene, Polyvinylalcohol	Multiple data sets taken >40 years apart, different laboratories, commercial samples – known MW, purity
Dextran	C, H, N analyses, TGA/DSC

Amorphous Pharmaceuticals and excipients



Amorphous Pharmaceuticals



Conclusions

- ICDD developed a series of tools and references for amorphous and nanomaterial analysis. These are embedded in the PDF-4/Organics database.
- Digital simulations for all crystalline references, from powders and single crystals
- Experimental digital data for non-crystalline materials

  (more details in presentation by T. Blanton)
- Established editorial guidelines for nanomaterials and amorphous materials

  (more details in presentation by S. Kabekkodu)
- Developed procedures for obtaining target pharmaceuticals and producing references

  (more details in presentation by J.Kaduk)

Thank You !

Singular, Allegra

ACKNOWLEDGEMENTS

Use of the Advanced Photon Source at Argonne National Laboratory was supported by the US Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357.

ICDD®

INTERNATIONAL CENTRE FOR DIFFRACTION DATA