THE DEVELOPMENT OF NANOMATERIALS AND AMORPHOUS REFERENCES AND THEIR USE IN PHARMACEUTICAL IDENTIFICATION AND CHARACTERIZATION

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

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Why develop nanomaterial or amorphous references

Most common analyses –global user surveys 2006, 2009, 2012

Material Identification

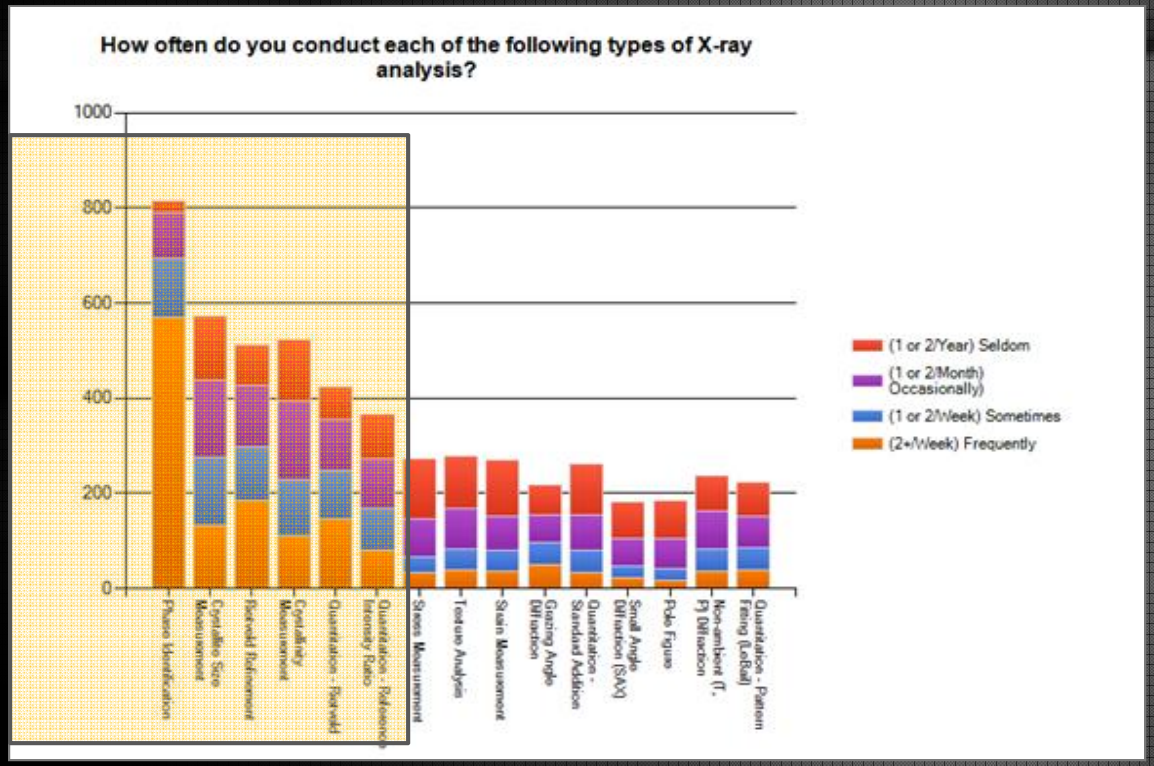
Material Quantitation

Rietveld

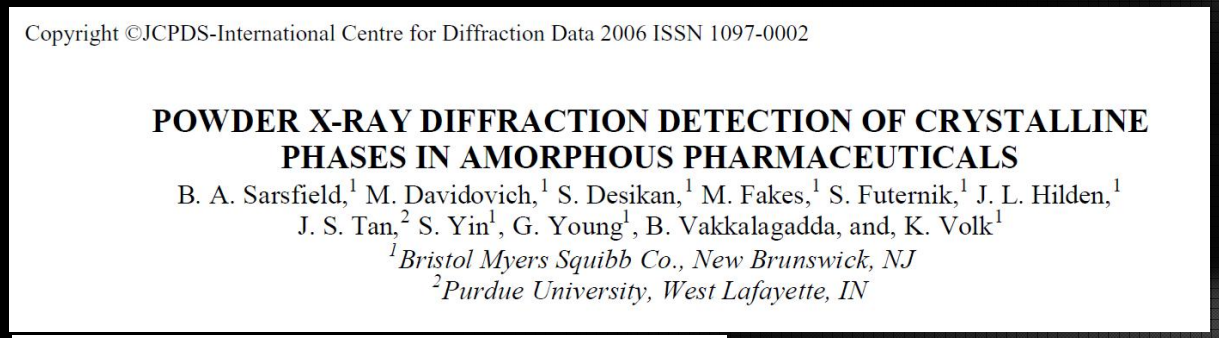
RIR

Crystallinity

Crystallite Size



Most Frequent Downloads



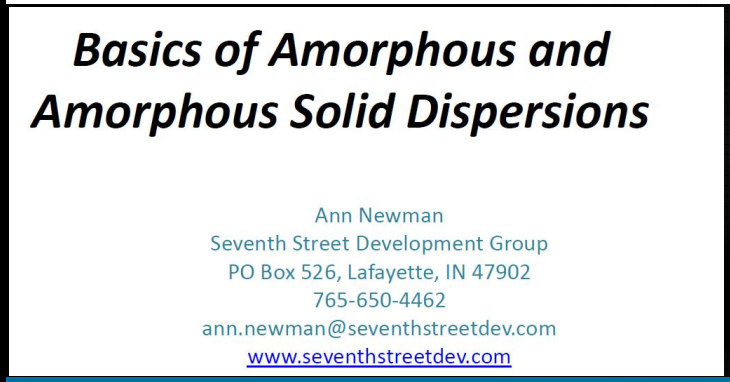
POWDER X-RAY DIFFRACTION DETECTION OF CRYSTALLINE PHASES IN AMORPHOUS PHARMACEUTICALS

B. A. Sarsfield,[1] M. Davidovich,[1] S. Desikan,[1] M. Fakes,[1] S. Futernik,[1] J. L. Hilden,[1] J. S. Tan,[2] S. Yin[1], G. Young[1], B. Vakkalagadda, and, K. Volk[1]

[1]*Bristol Myers Squibb Co., New Brunswick, NJ*

[2]*Purdue University, West Lafayette, IN*

Advances in X-ray Analysis
on-line publications



Basics of Amorphous and Amorphous Solid Dispersions

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PPXRD on-line presentations

Characterisation and prediction of stability of amorphous materials during pharmaceutical development: Pair-wise Distribution Function

Helen Blade, Steve Cosgrove, Jonathon Booth, Anne Kavanagh

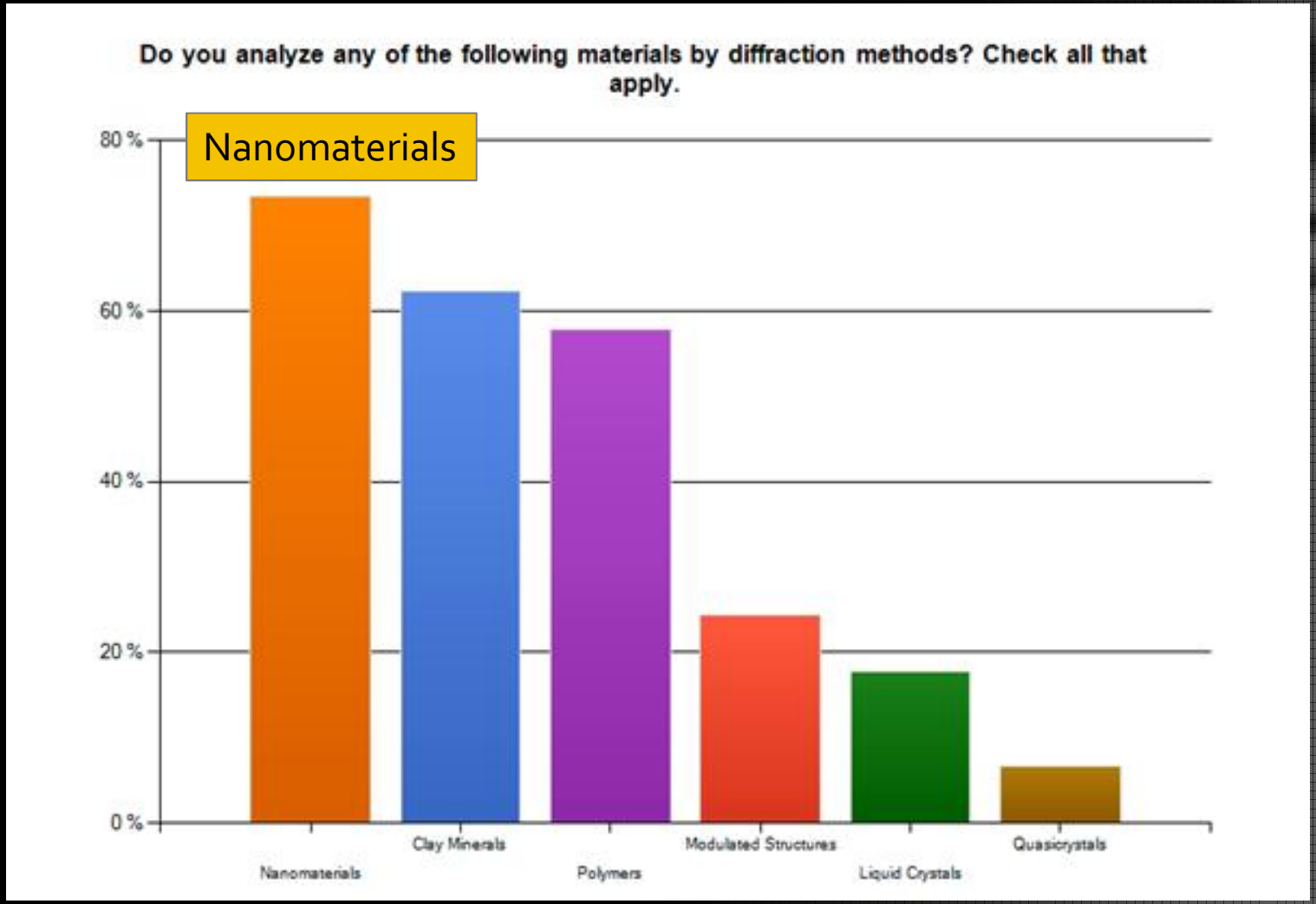
PAR&D, AstraZeneca, Macclesfield, UK

May 2009

AstraZeneca
life inspiring ideas

PPXRD on-line presentations

PDF-4/Organics



Tools for Nanomaterial and Amorphous Analyses with PDF-4+ Databases

Experimental

Amorphous references

Nanomaterial references

Supporting Data

- DSC/TGA
- SEM/TEM
- Pair Distribution Functions

Calculation

Digital Pattern Simulation

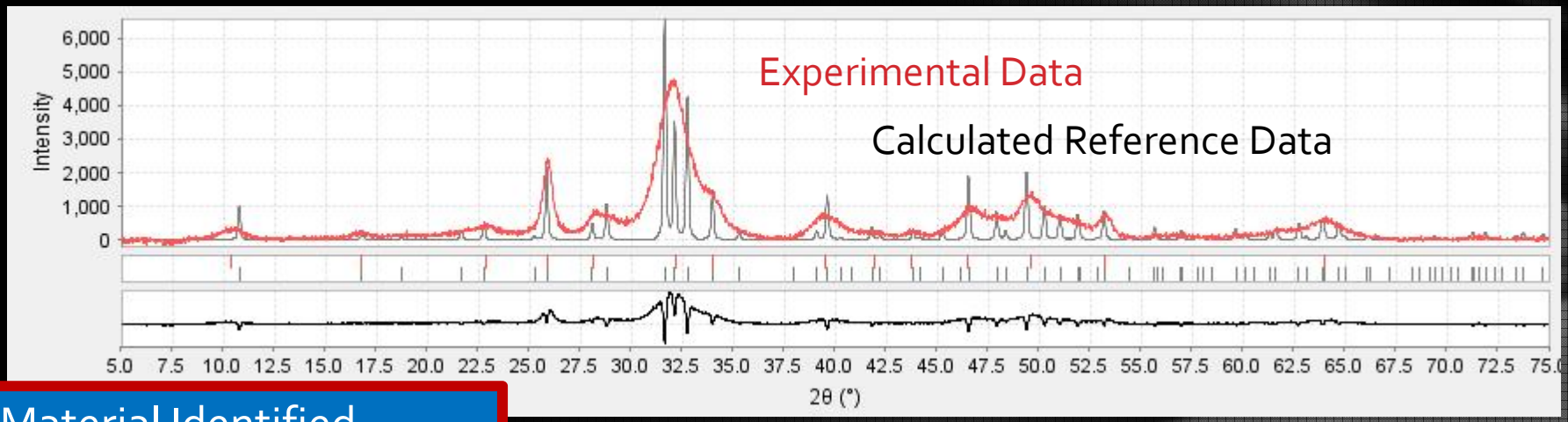
- Use 3 basic Algorithms
- **Applied Instrument Functions**
- **Crystallite Size Modeling**
- **Molecular Orientation Functions**

X-ray, neutron and electron diffraction scattering factors

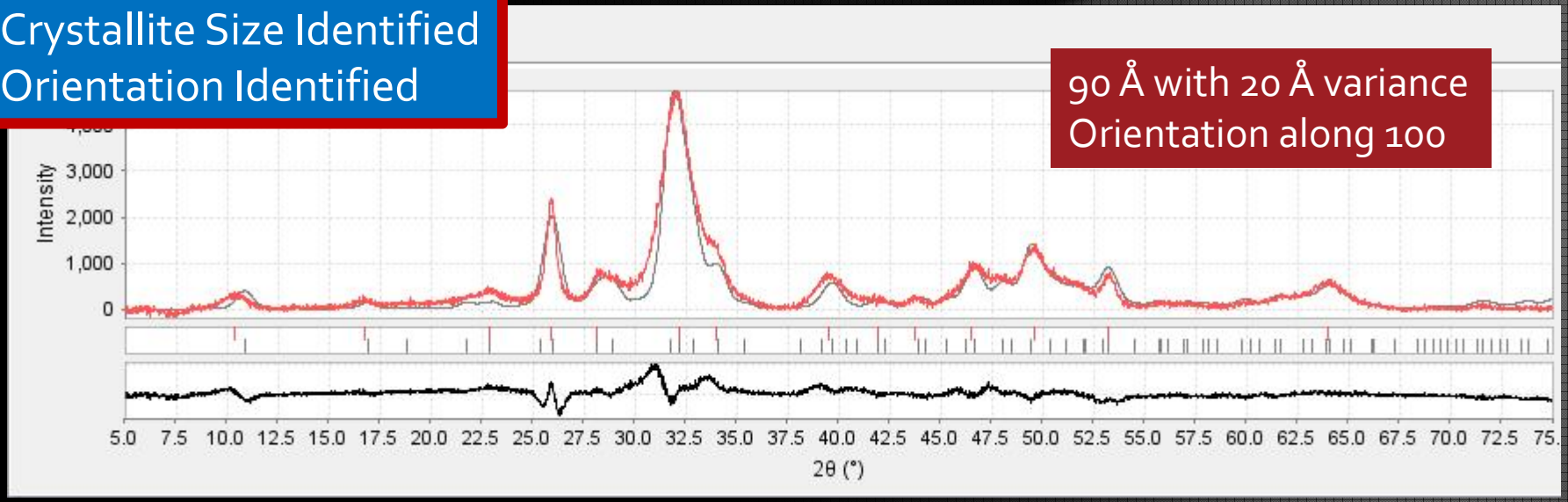
Spot, ring, EBSD pattern simulation

Similarity indices for identification of amorphous materials

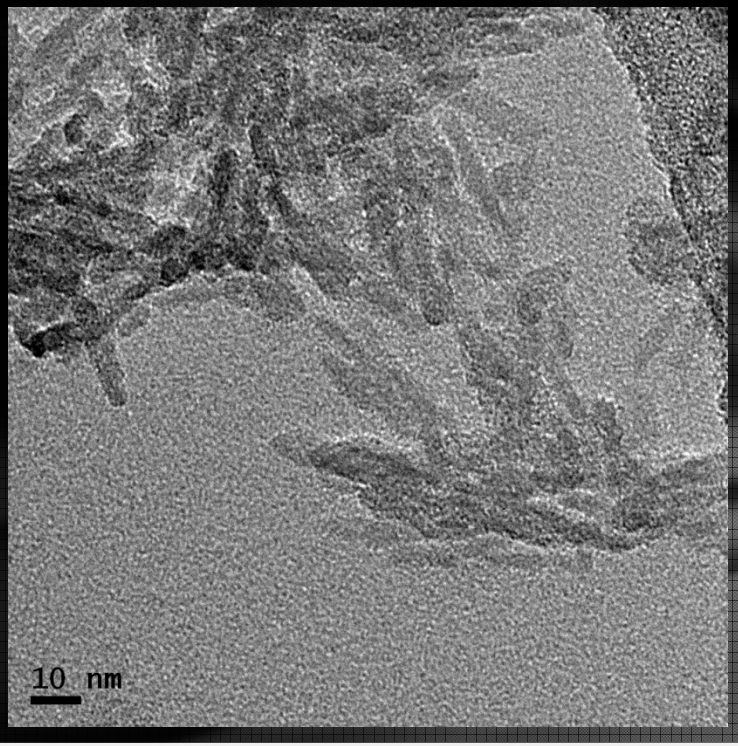
Calculation Tools - Hydroxyapatite

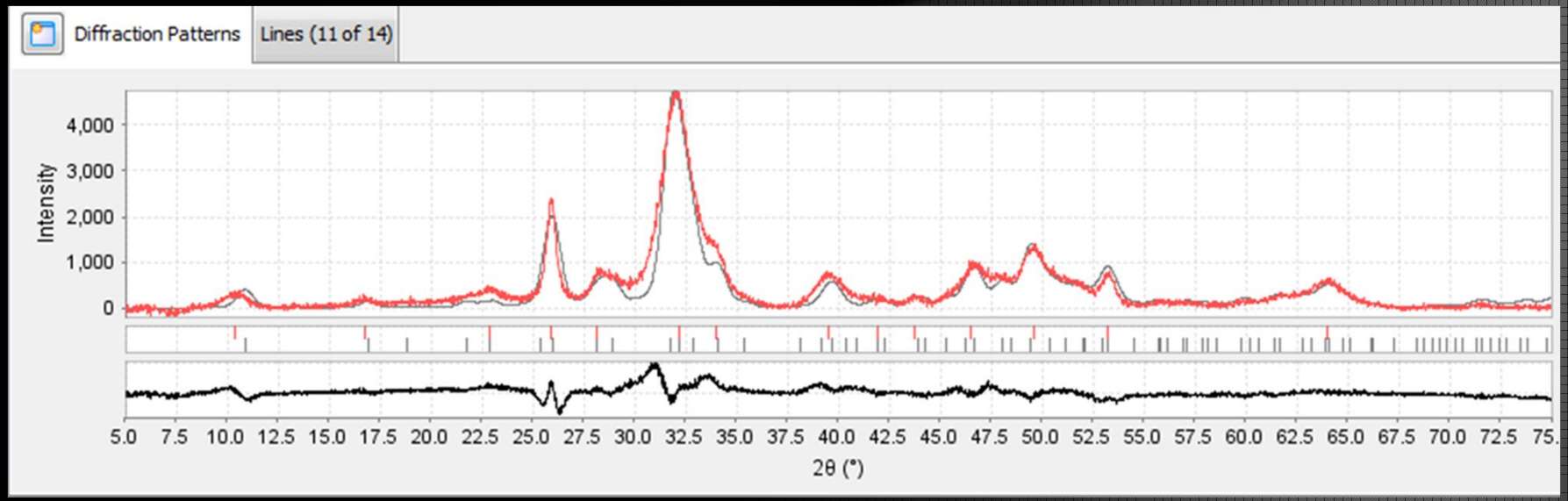


Material Identified
Crystallite Size Identified
Orientation Identified

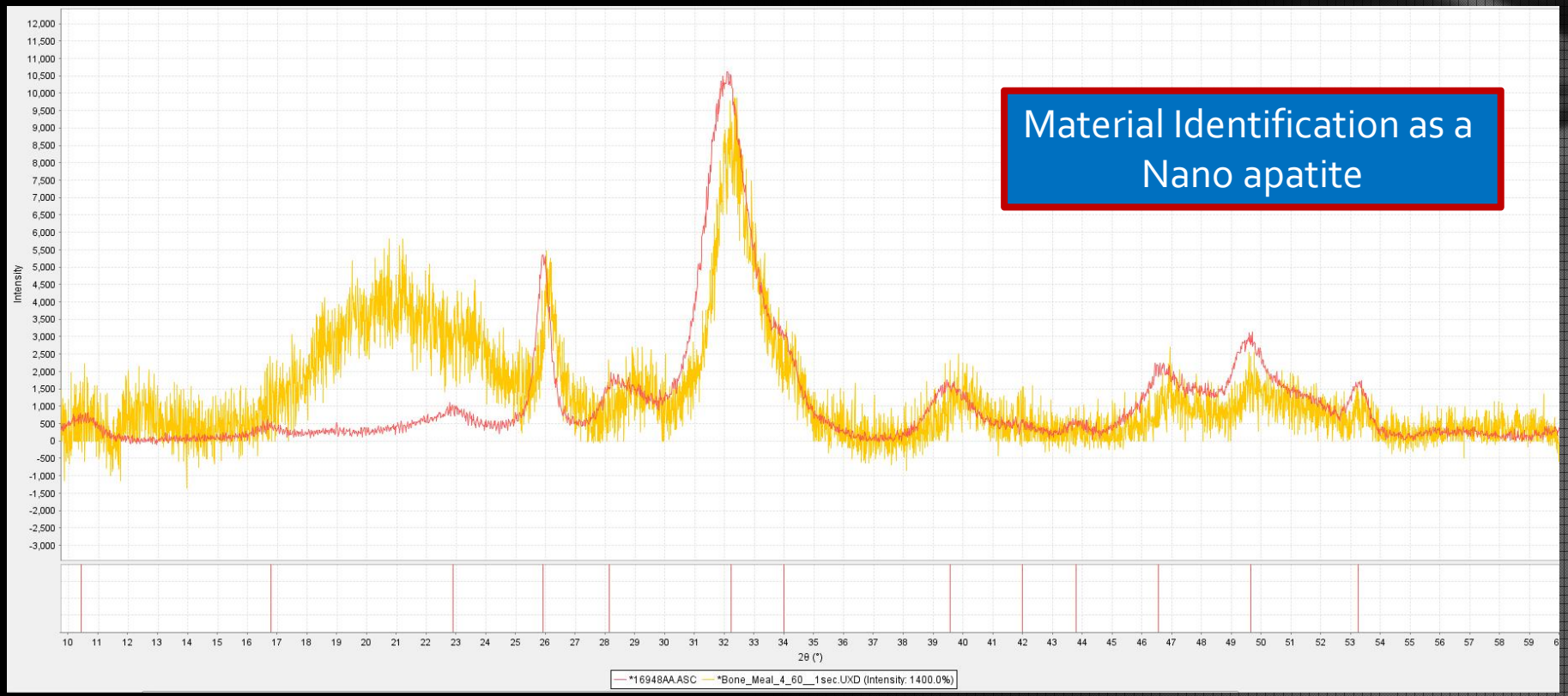


Hydroxyapatite

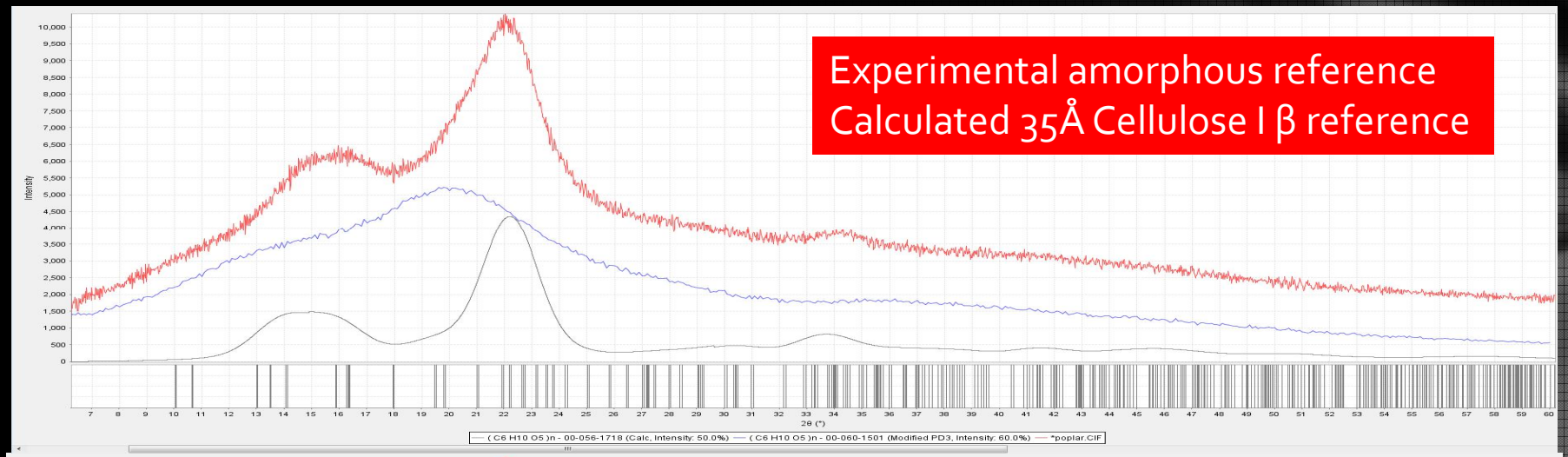


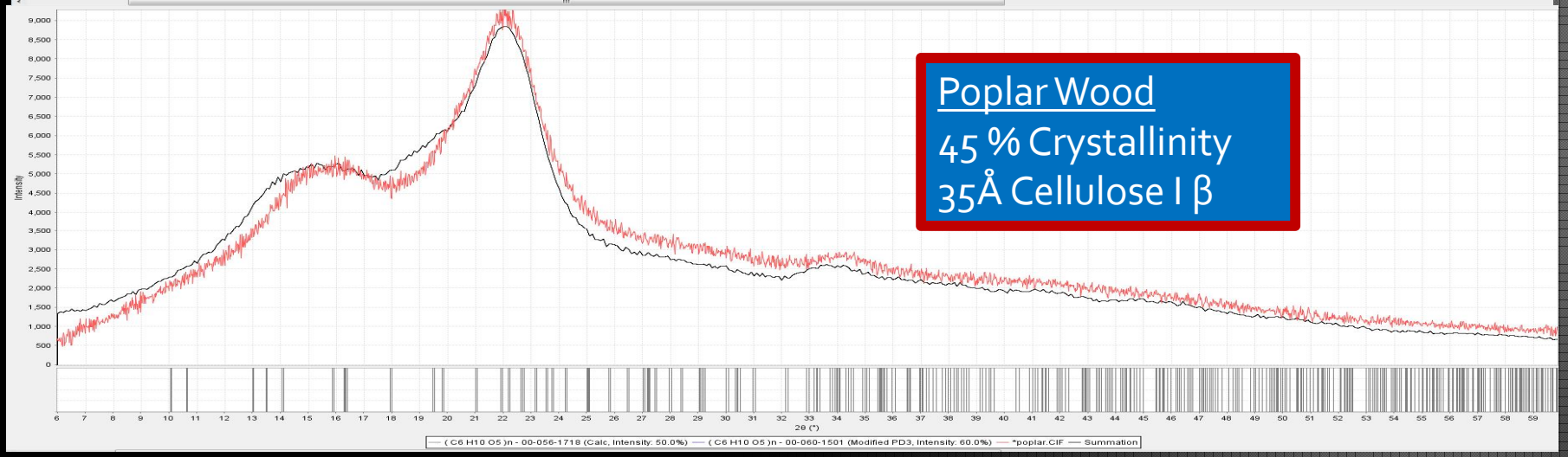


Experimental Tools - Nanoapatite Reference vs Commercial Bone Meal Fertilizer



Combine experimental and calculation tools – Poplar Wood





Reference materials for the study of polymorphism and crystallinity in cellulosics

T. G. Fawcett,[1,a)] C. E. Crowder,[1] S. N. Kabekkodu,[1] F. Needham,[1] J. A. Kaduk,[2] T. N. Blanton,[3] V. Petkov,[4] E. Bucher,[5] and R. Shpanchenko[6]

[1]*International Centre for Diffraction Data, Newtown Square, Pennsylvania*
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[5]*International Paper Company, Loveland, Ohio*
[6]*Moscow State University, Moscow, Russia*

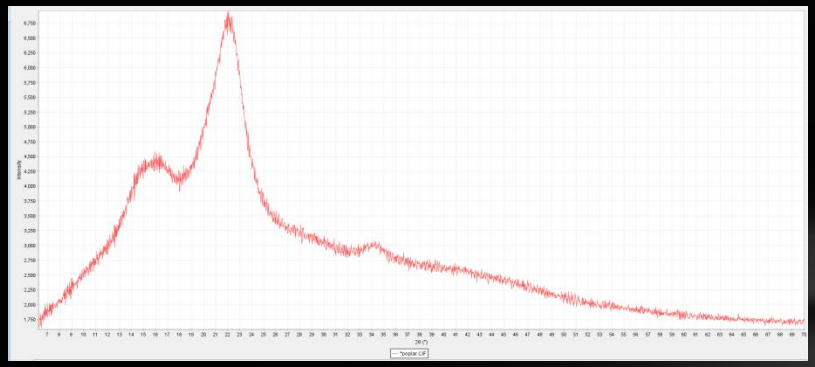
Powder Diffr., Vol. 28, No. 1, March 2013

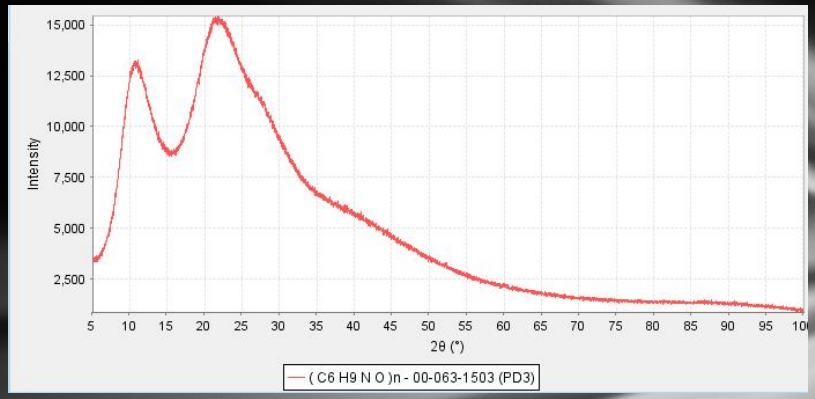
TABLE II. PDF cellulosic reference materials.

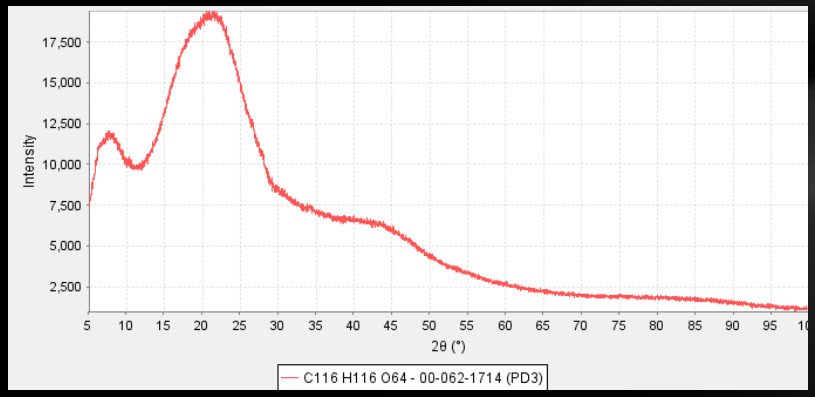
Material	PDF entry	Key attributes/source
Cellulose Iα	00–056–1719	Structural determination derived from fiber
Cellulose Iβ	00–056–1718	Structural determination derived from filter paper
Cellulose II	00–056–1717	Structural determination derived from fiber
Amorphous cellulose	00–060–1501	Derived from cryogrinding multiple specimens
Microcrystalline cellulose	00–060–1502	Predominately cellulose I β, 40 Å Sigma Aldrich
Amorphous cellulose acetate	00–061–1408	Oriented amorphous
Cellulose acetate, CTA II	00–061–1407	Enhanced crystallinity
Cellulose acetate, CTA II	00–061–1409	Oriented film
Cellulose acetate	00–062–1713	USP grade
Cellulose acetate butyrate	00–062–1712	USP grade
Cellulose acetate pthalate	00–062–1714	USP grade
Methylcellulose	00–062–1290	Production grade
Methylcellulose	00–062–1291	Dehydrated production grade

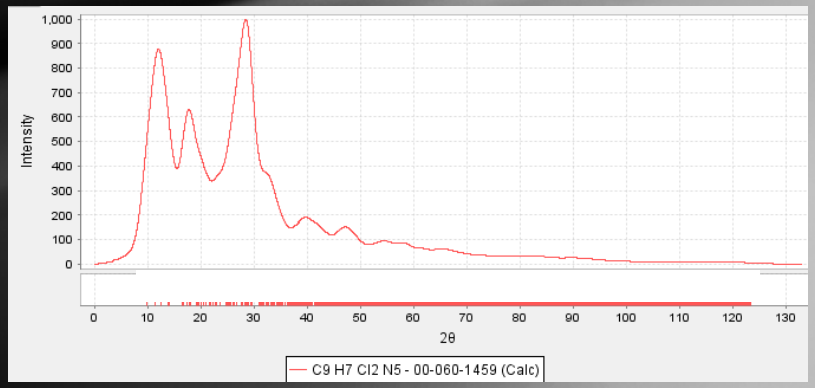
Amorphous or Nanocrystalline ?

Incoherent scatter or small (50 Å <) crystallite scatter ?





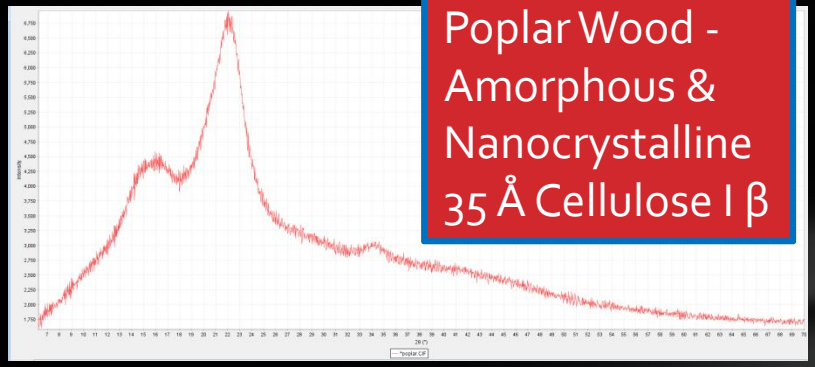




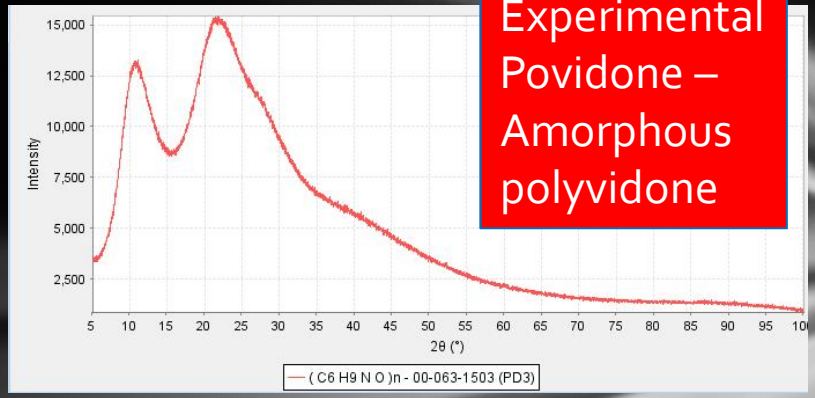
Where is the background ?

Amorphous or Nanocrystalline ?

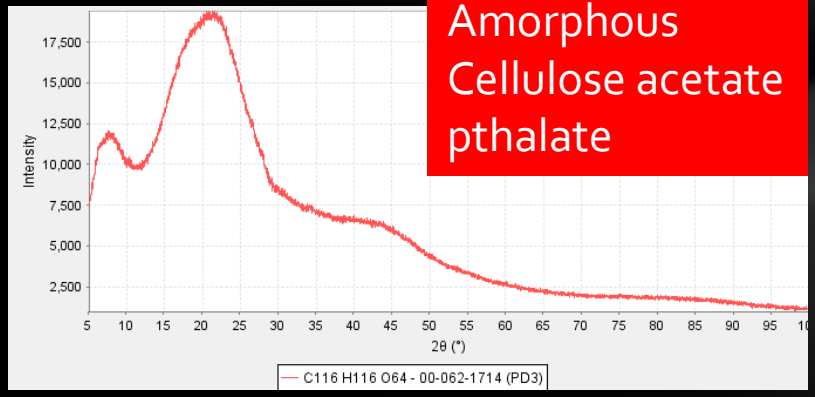
Experimental Poplar Wood - Amorphous & Nanocrystalline 35 Å Cellulose I β



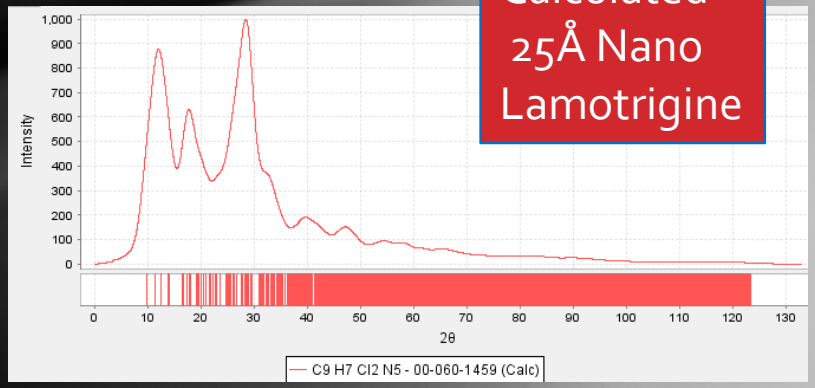
Experimental Povidone – Amorphous polyvidone



Experimental Amorphous Cellulose acetate pthalate

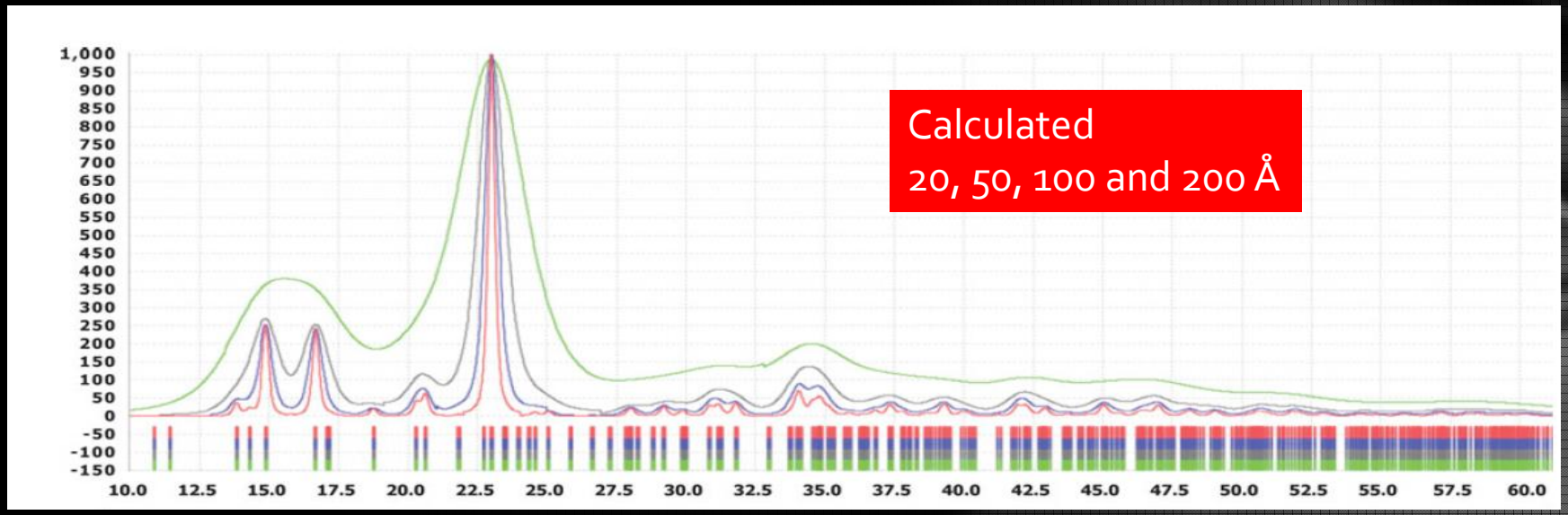


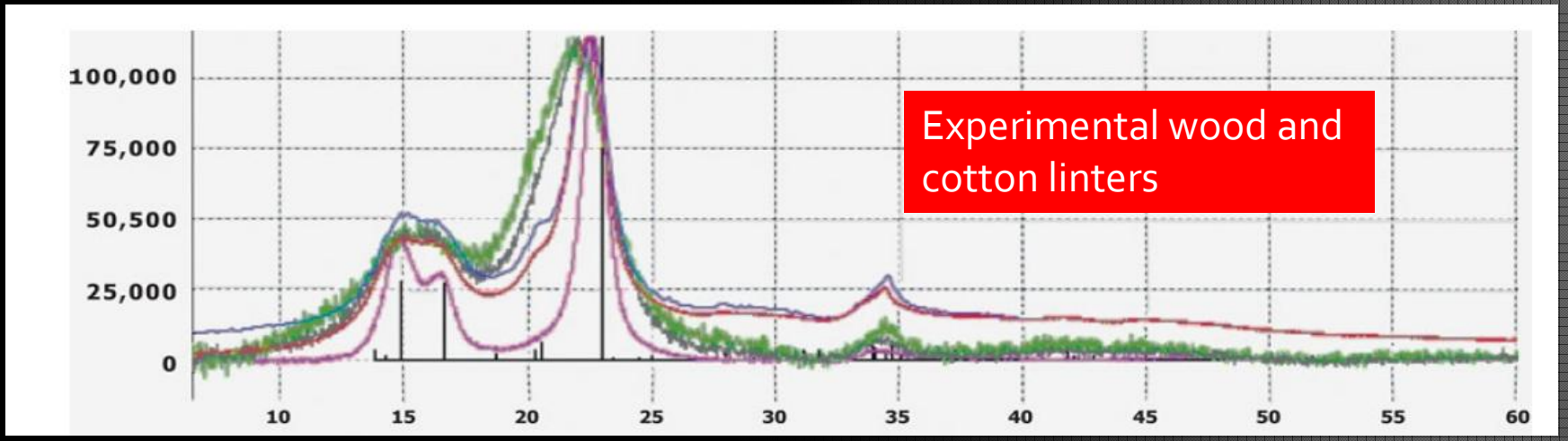
Calculated 25Å Nano Lamotrigine



Where is the background ?

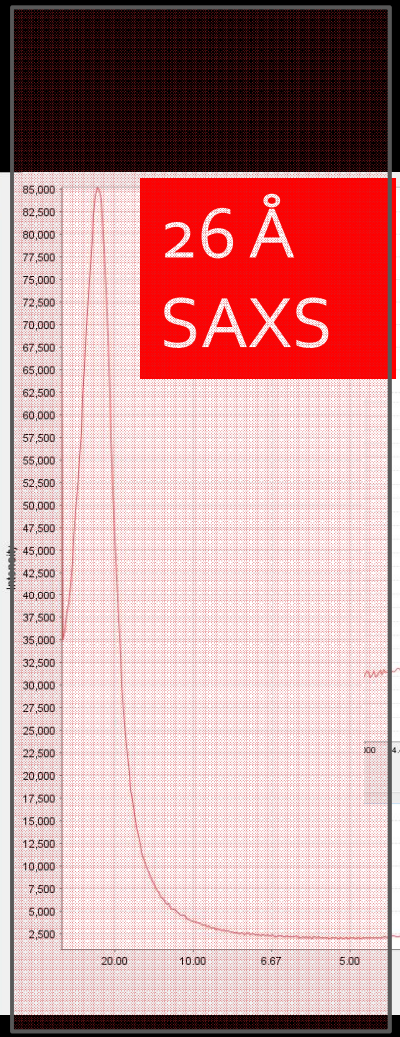
Cellulose Iβ

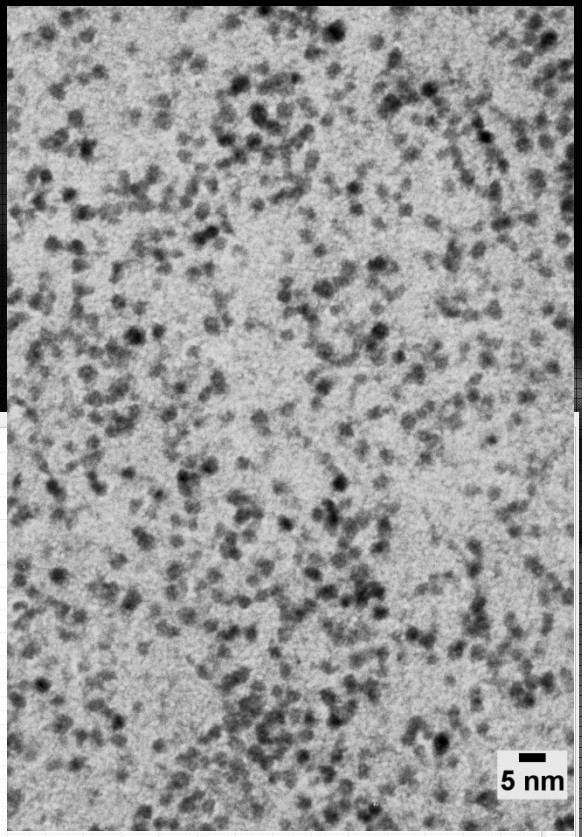




Nano Ceria

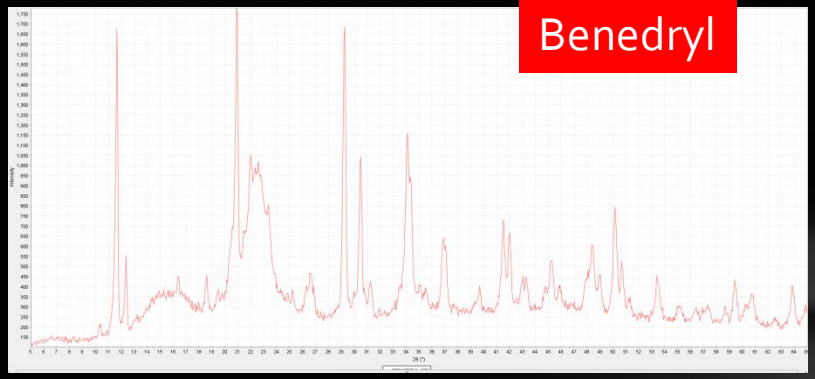
Nanomaterials would be expected to have SAXS at low angle from particle scattering



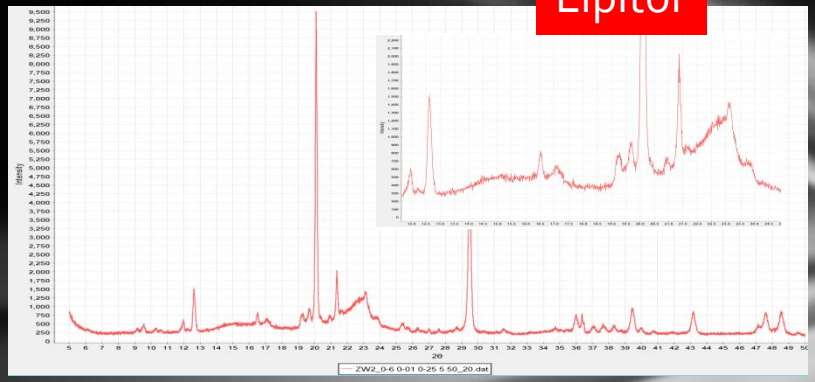


Pharmaceutical Formulations

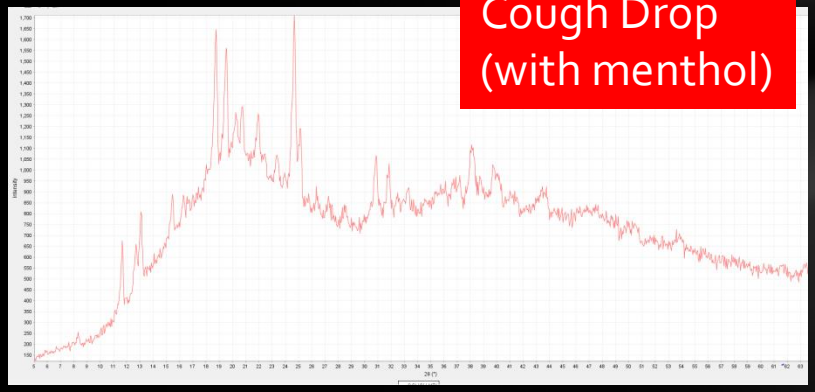
Benedryl



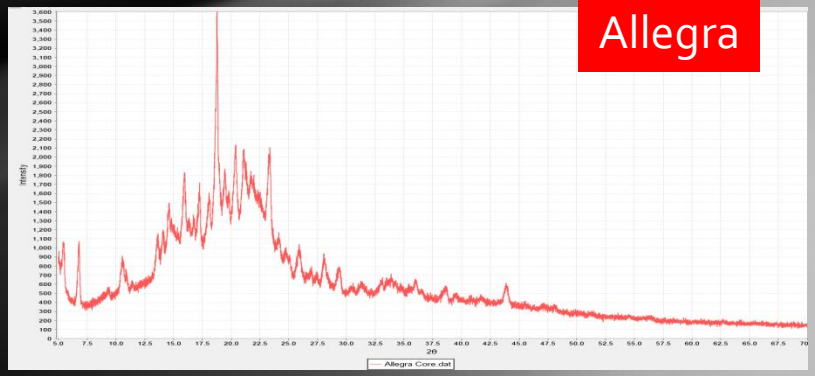
Lipitor



Cough Drop (with menthol)

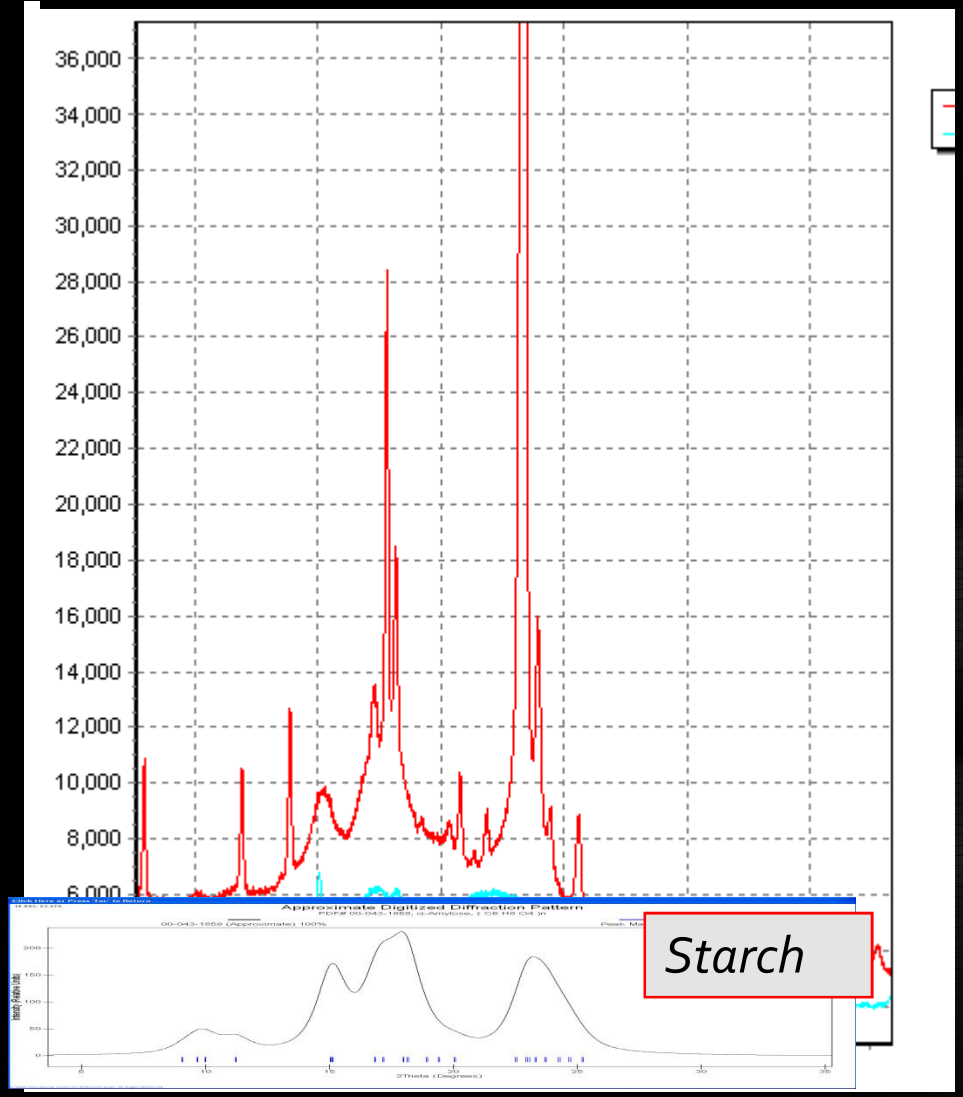


Allegra

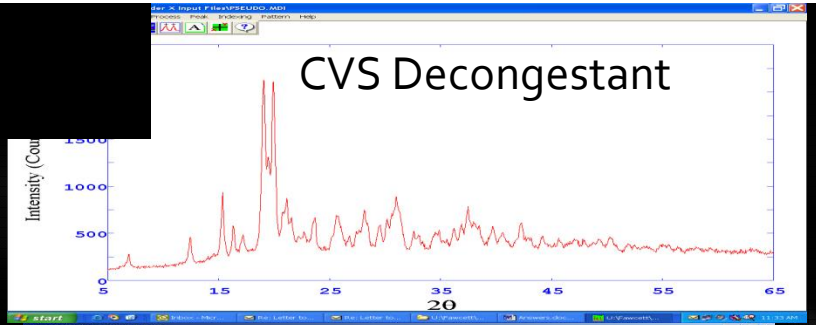


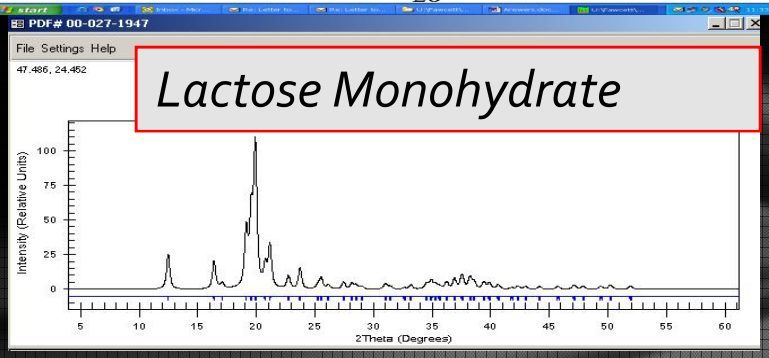
Nanocrystalline and/or amorphous components are very common

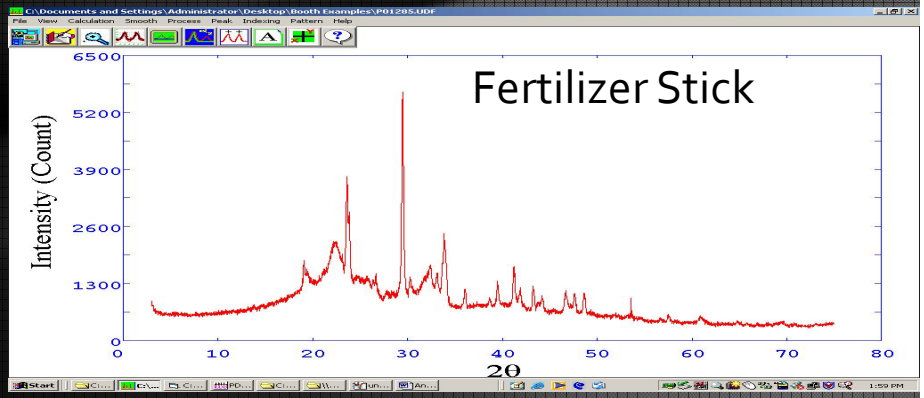
Micronized Ingredients

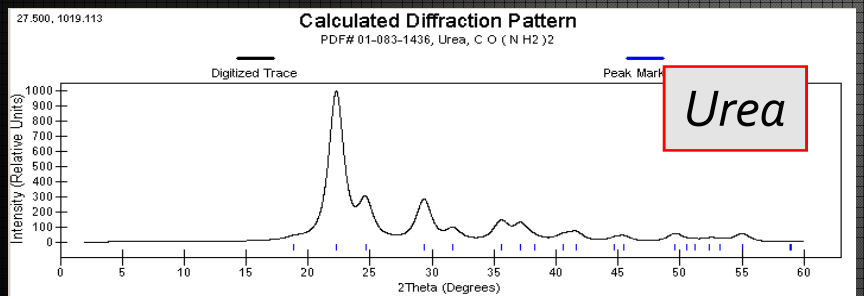


Lipoic Acid in rice flour (top)





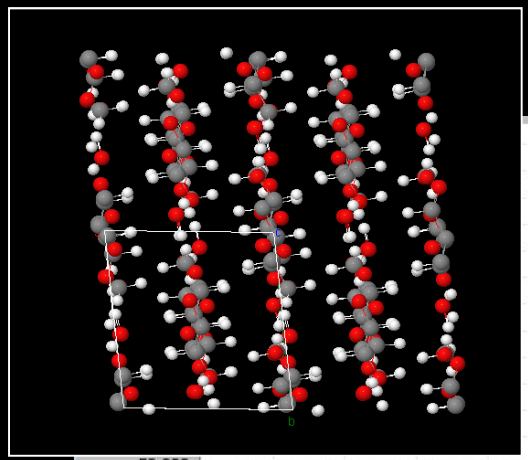




Amorphous or Nanocrystalline ? Incoherent scatter or small (50 Å <) crystallite coherent scatter ?

Use of supplemental analytical data

Microcrystalline Cellulose - Digital pattern simulation from the crystal structure

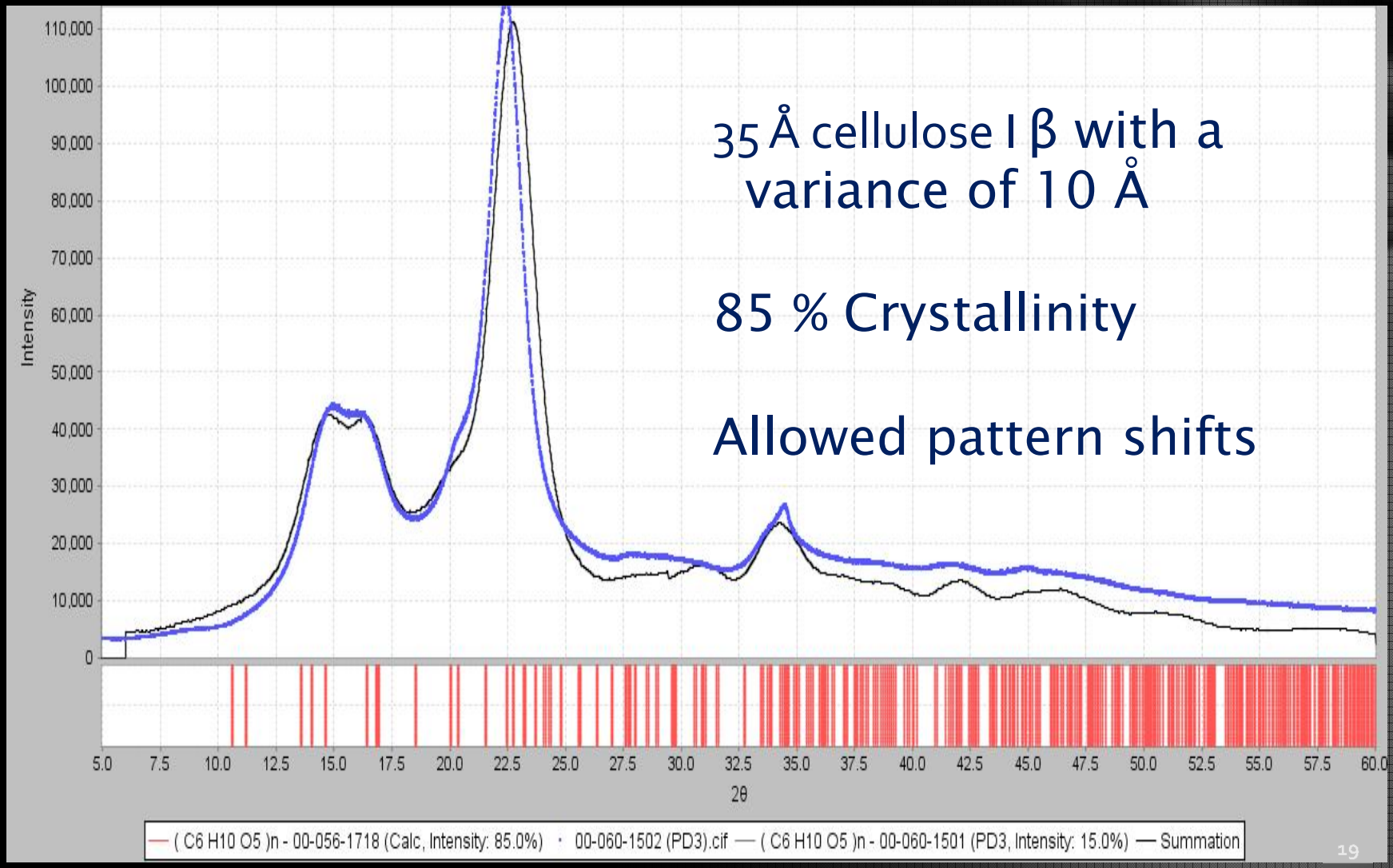


1) Experimental Data in Blue

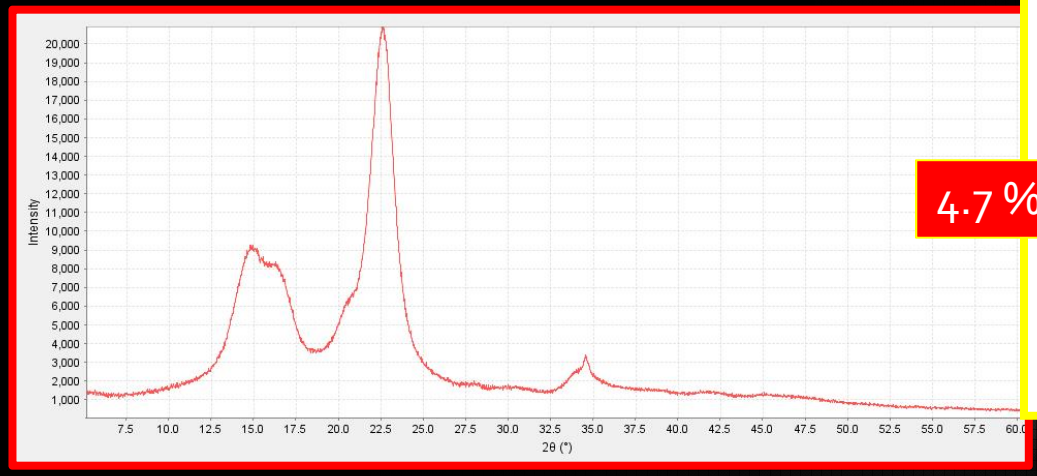
2) 35 Å simulation of Cellulose I β calculated from the crystal structure PDF 00-056-1718

3) Experimental digital patttern of amorphous cellulose PDF 00-060-1502

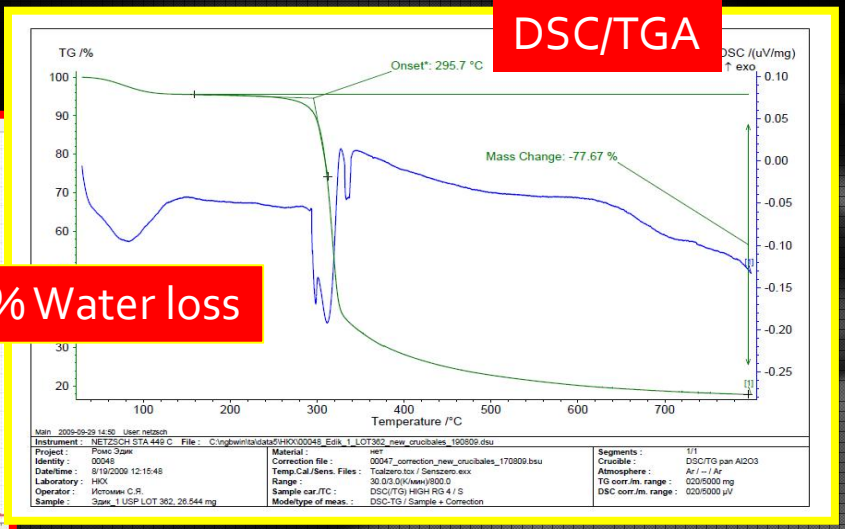
Sigma-Aldrich microcrystalline cellulose – crystallite size and crystallinity



Supplemental Data – USP Microcrystalline Cellulose



DSC/TGA

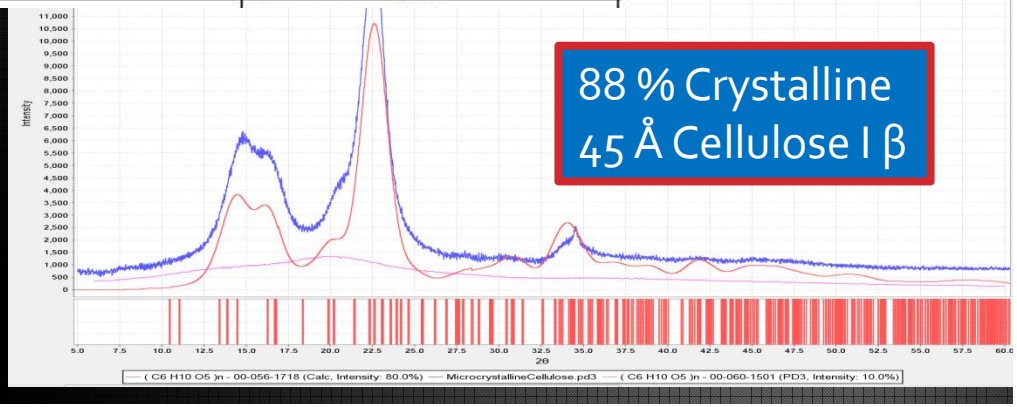


4.7 % Water loss

Sample designation	Sample name	Nominal composition (from MSDS)	Elemental composition, %
FOD 362	Microcrystalline cellulose	$(C_6H_{10}O_5)_n$	C – 42.35(6) H – 6.23(1)

Weight %: C44.45 H6.22 O49.34

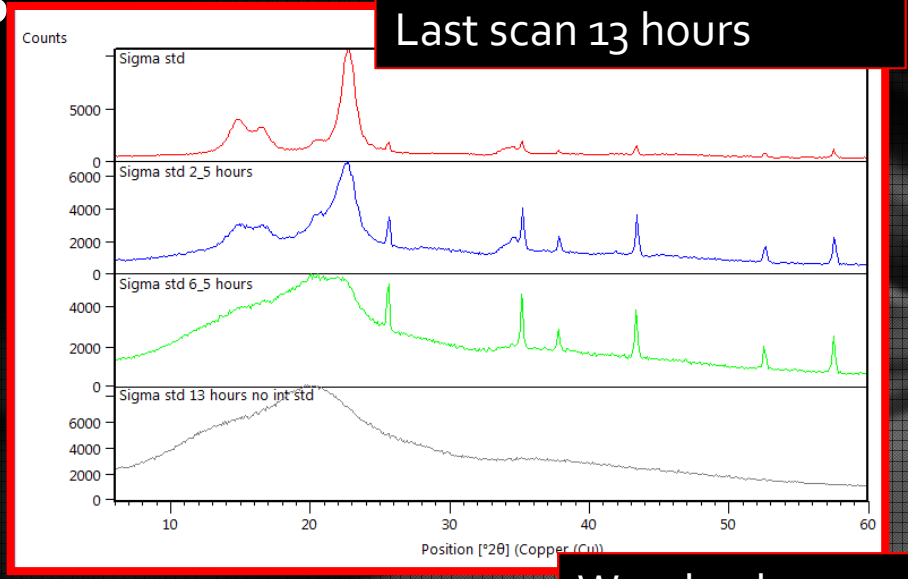
95 % of expected carbon



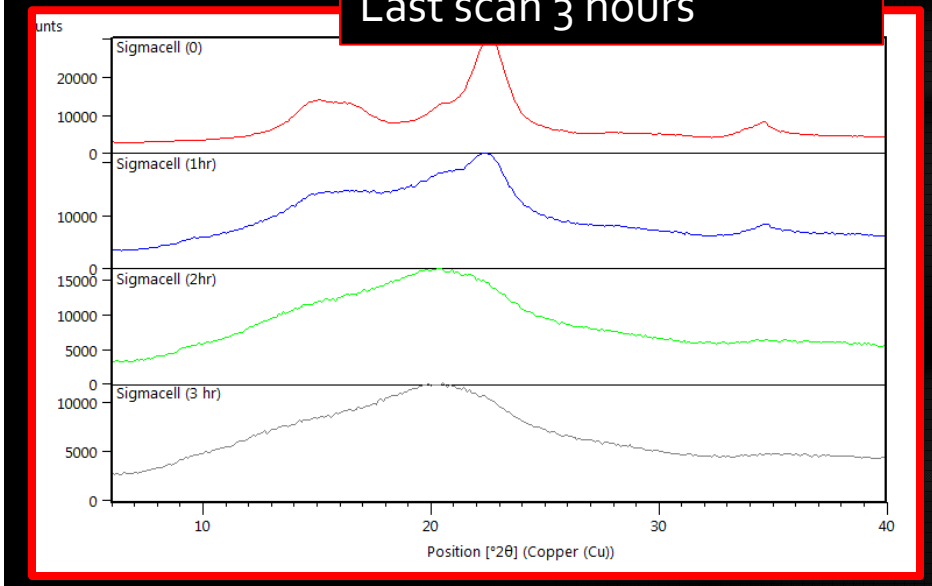
88 % Crystalline
45 Å Cellulose I β

Amorphous Cellulose – Use of multiple cyrogrinding samples

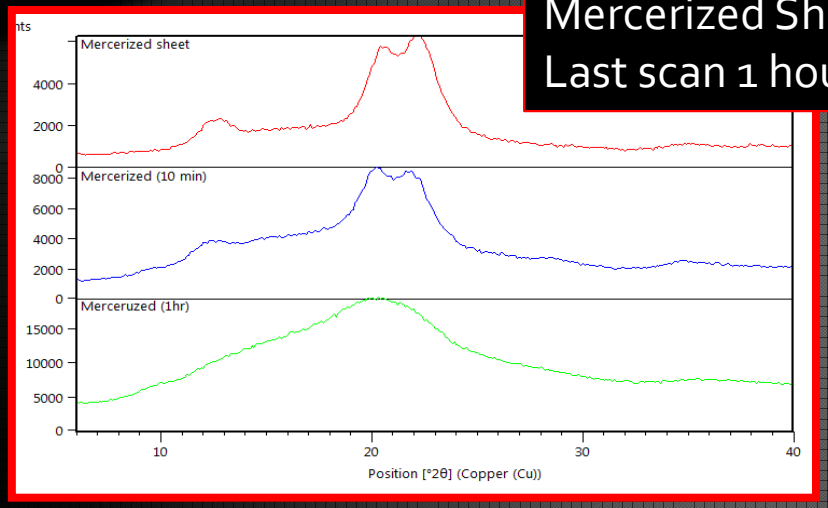
Cotton Linters –Source 1
Last scan 13 hours



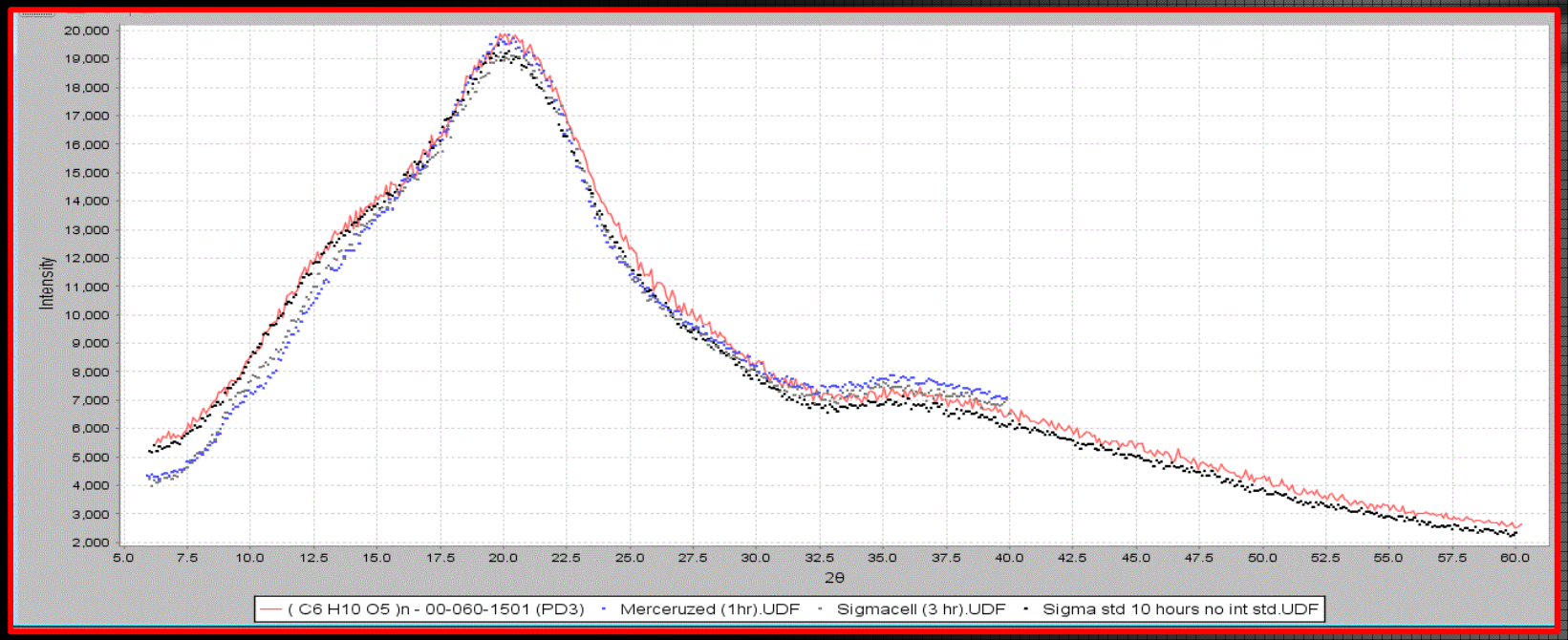
Cotton Linters – Source 2
Last scan 3 hours



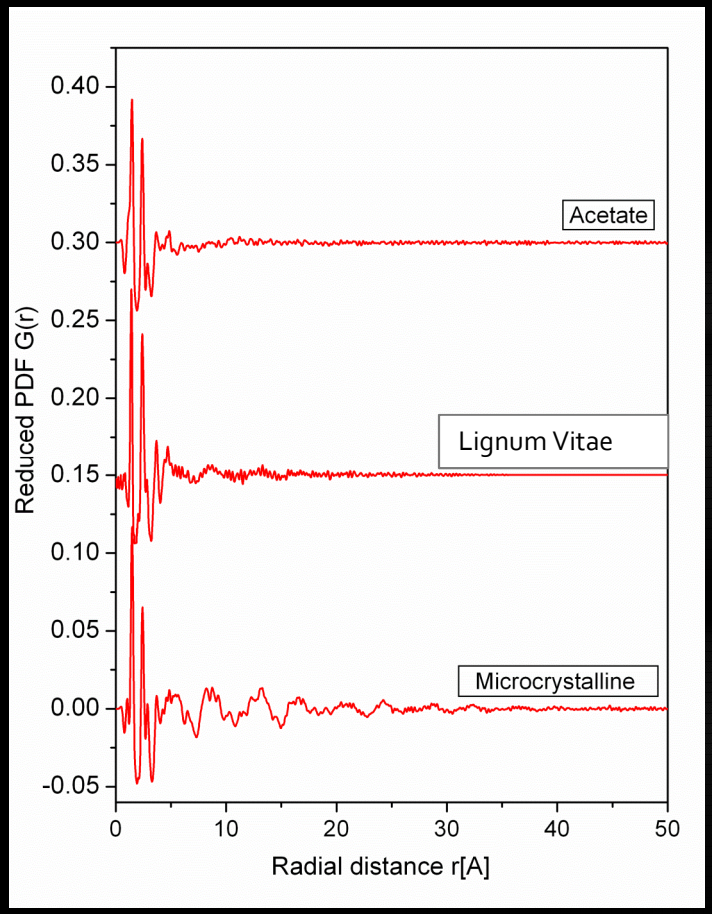
Wood pulp
Mercerized Sheet
Last scan 1 hour



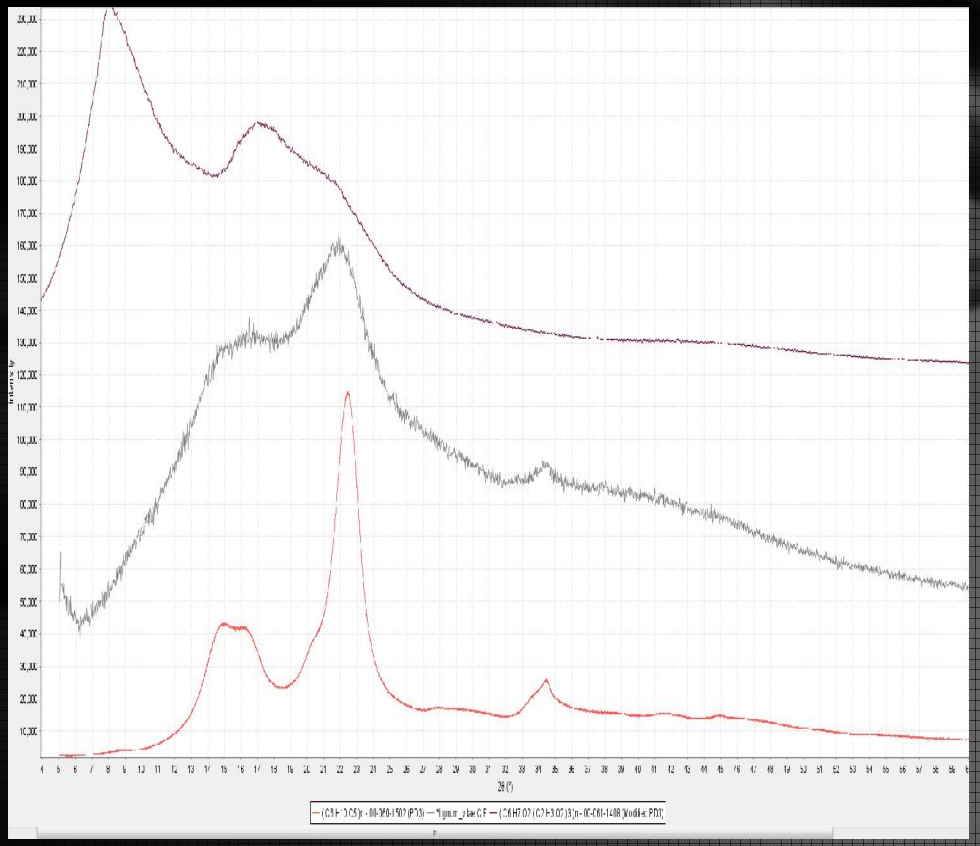
Amorphous cellulose – last data set of the 3 cryogrinding studies



Celluloses
- Domain size and crystalliniity



PDF



XRD

N-vinyl-2-pyrrolidone (Povidone)
Water soluble polymers

Sample	Water absorbed	Decomposition T, °C	Comments (weight loss up to 800°C)
FOC194	-5.3% (30-200C)	276.3 387.2	2 step decomposition: total weight loss - 88.98%
G2E126	-9.51% (30-200C)	373.8	1 step decomposition weight loss - 85.15%
F2H326	-13.51% (30-200C)	377.2	1 step decomposition total weight loss - 80.34%

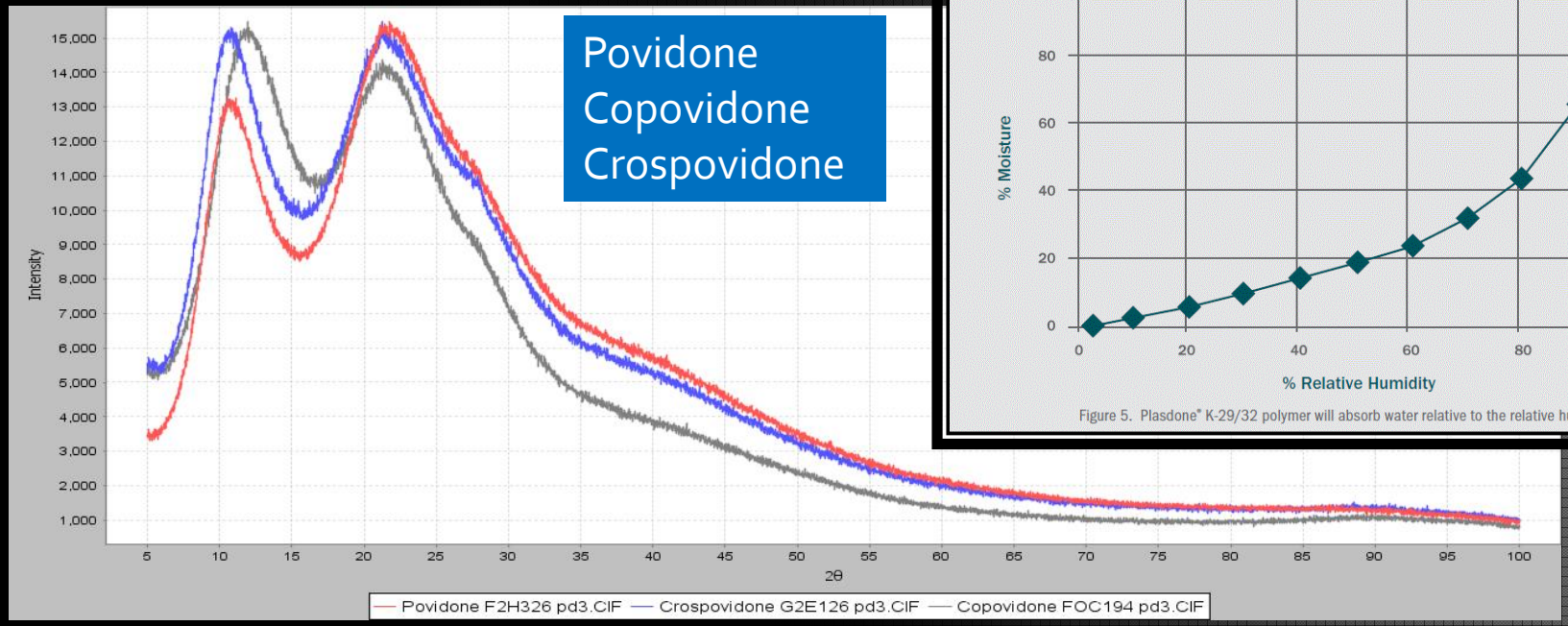
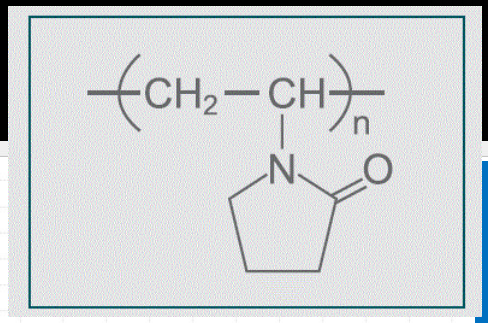


Figure 5. Plasdone® K-29/32 polymer will absorb water relative to the relative humidity.

Povidone Hydration



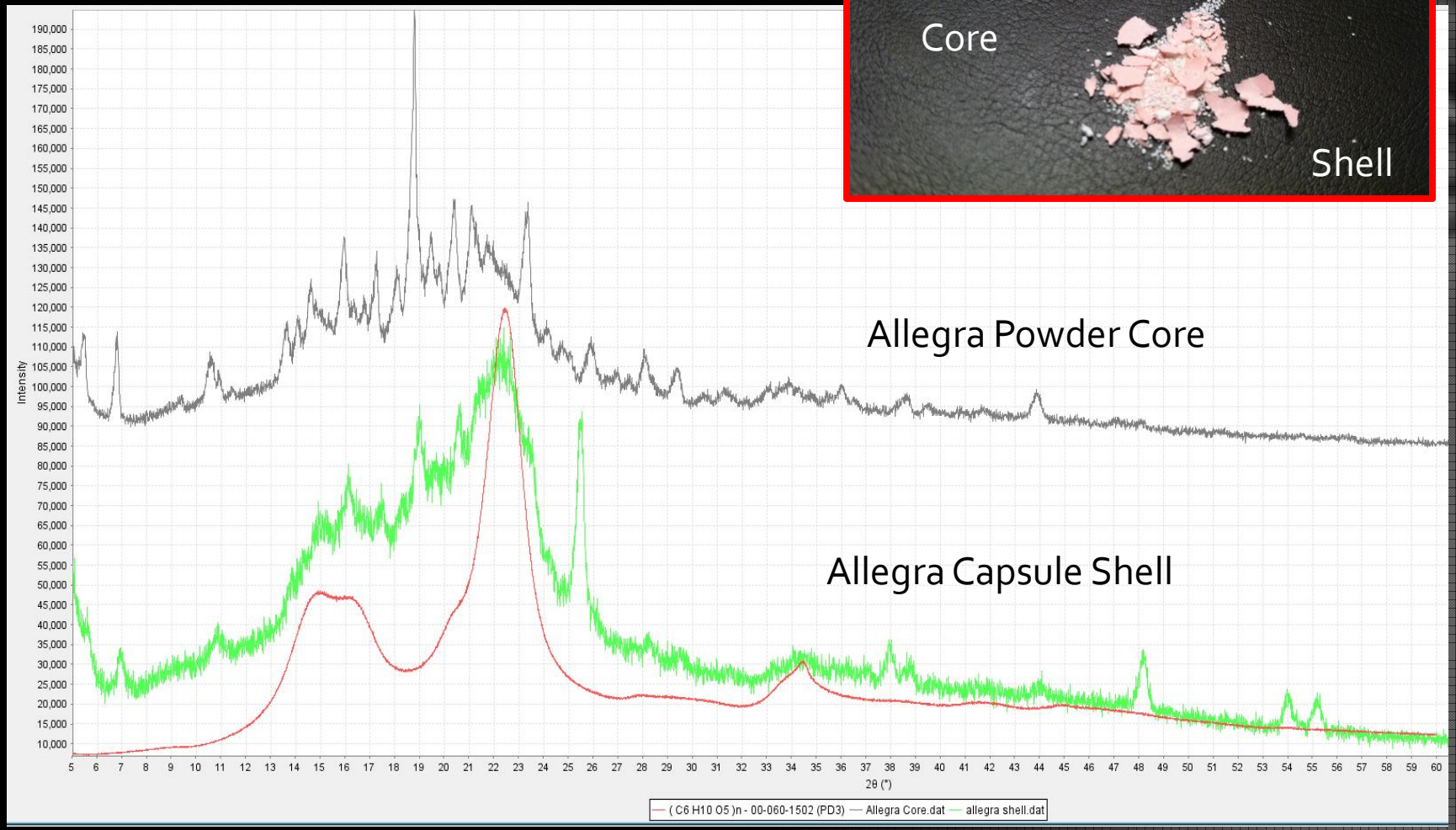
Red = Povidone, most water, 13.5 %
Homopolymer

Green = Crospovidone, 9.5 %
Crosslinked homopolymer

Grey = Copovidone, least water, 5.3 %
5 % vinyl acetate

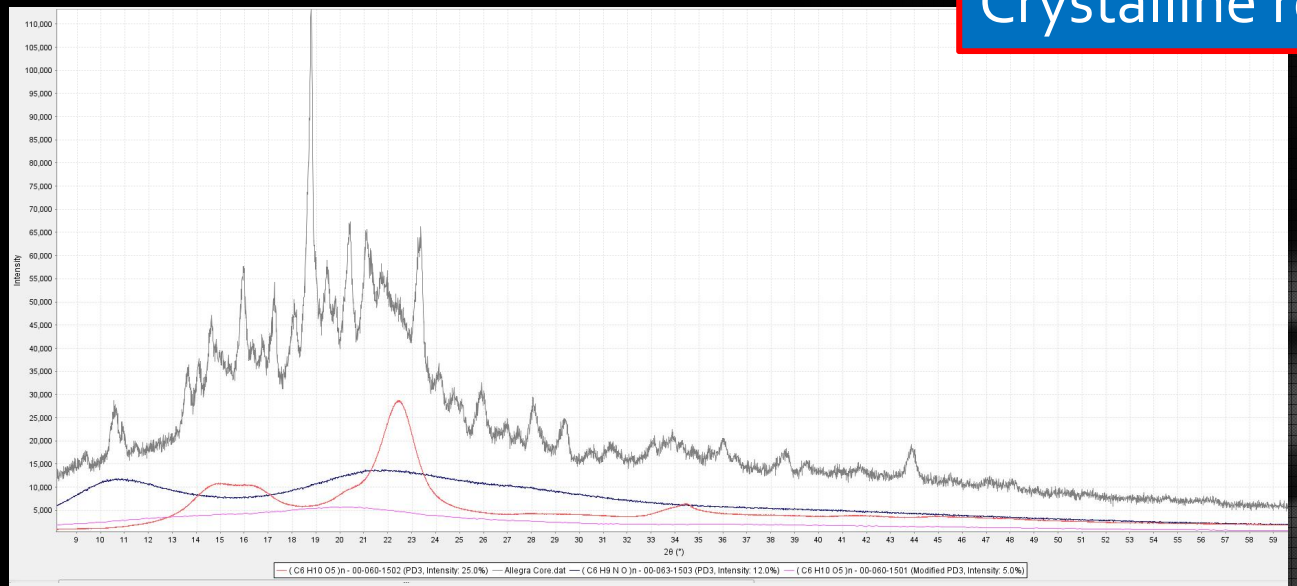
Allegra

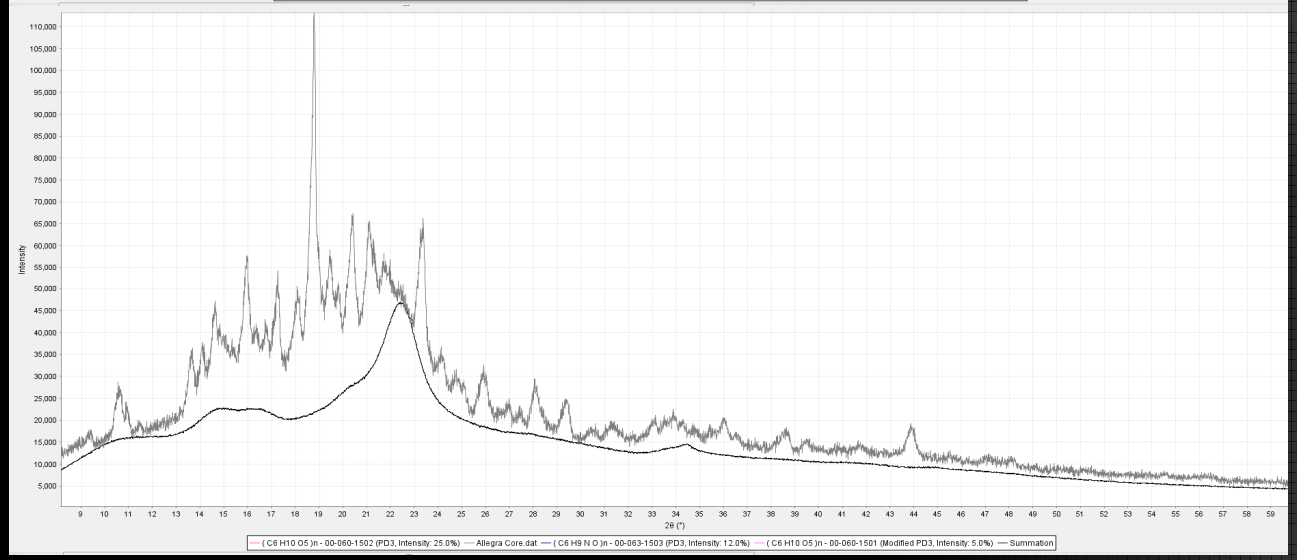

Core
Shell


Intensity
2θ (°)
Allegra Powder Core
Allegra Capsule Shell
(C6 H10 O5)n - 00-060-1502 (PD3)
Allegra Core.dat
allegra shell.dat

Allegra Core

Material Identification Using Amorphous and Nano Crystalline references

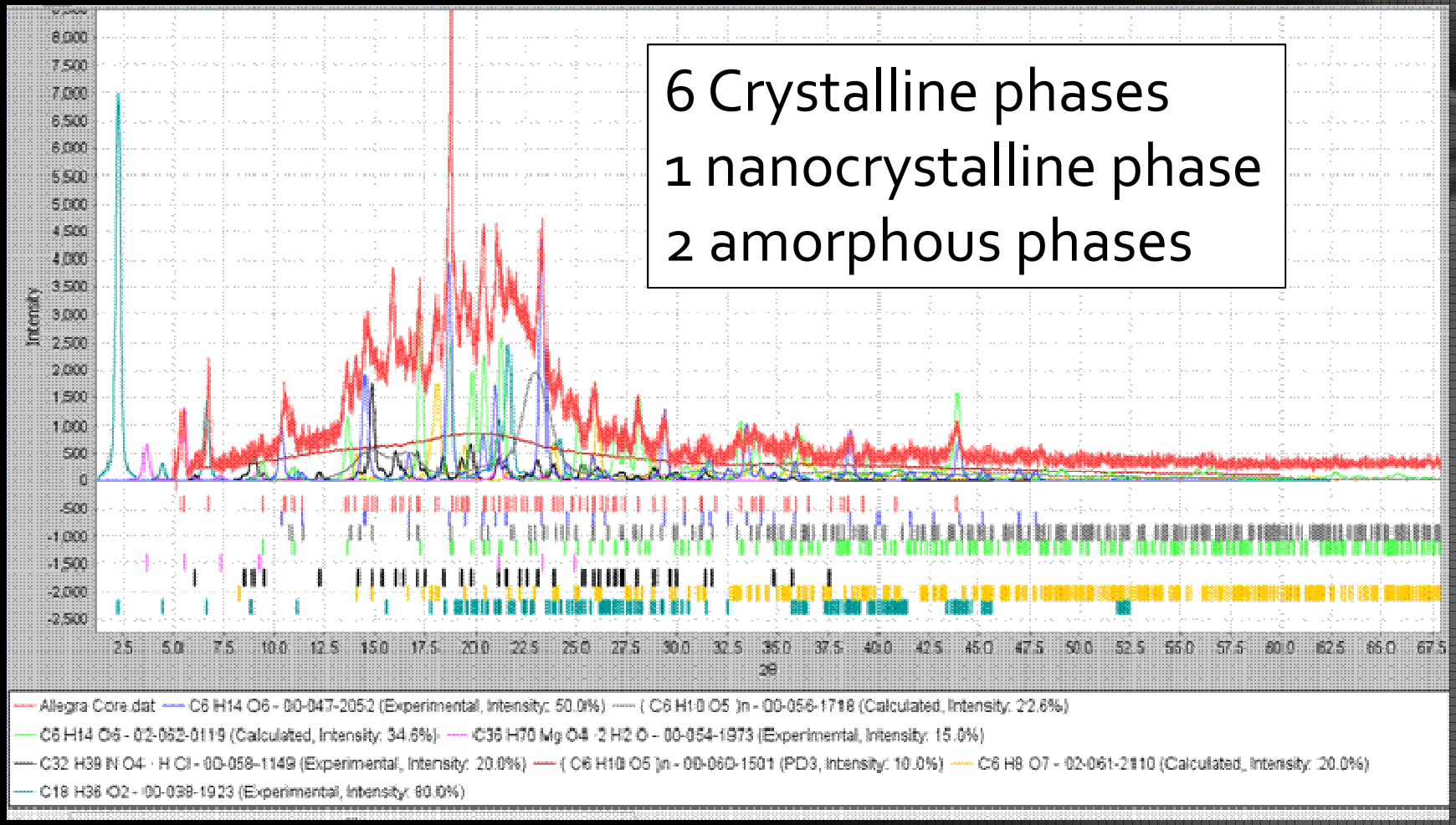




Microcrystalline Cellulose
Amorphous Cellulose
Amorphous Povidone

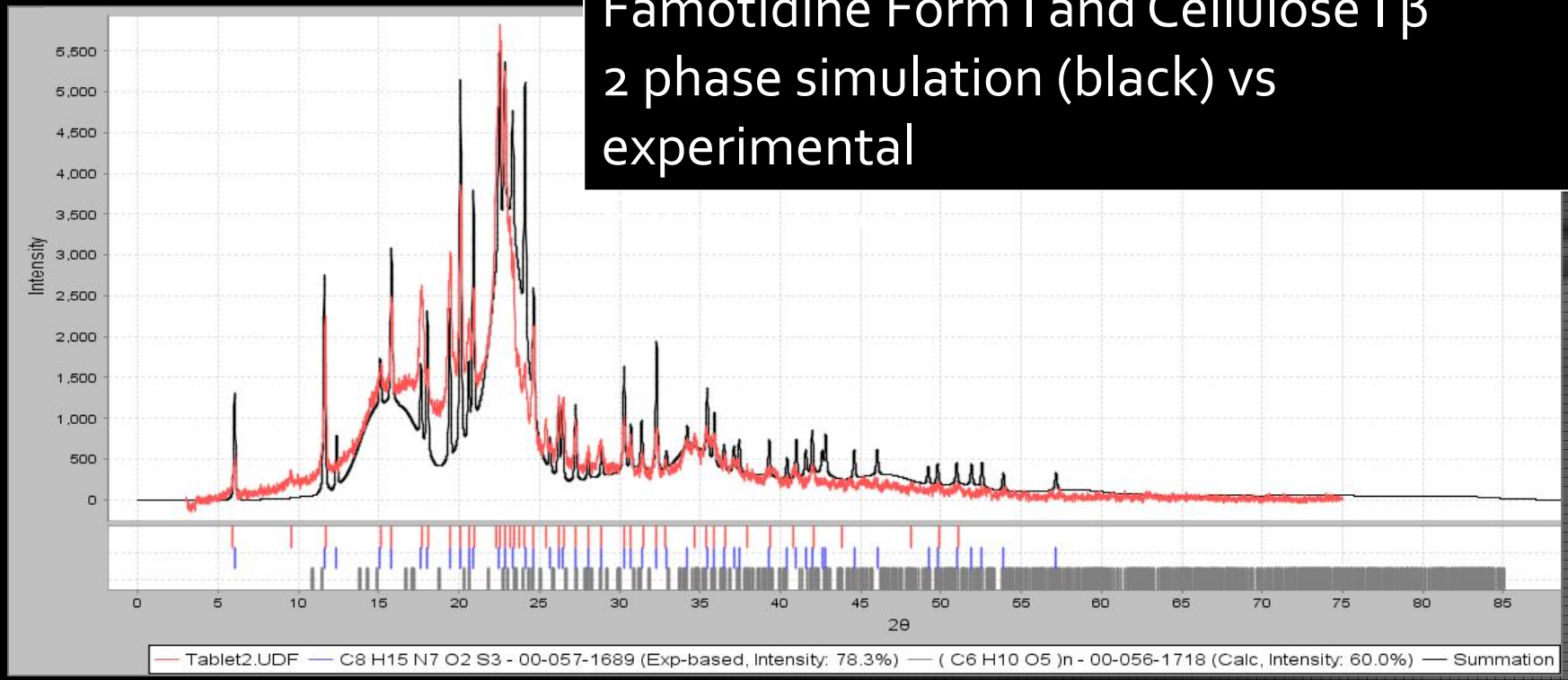
Summed Phases

9 phase Pharmacuetical Tablet
- Allegra, Uses all Tools



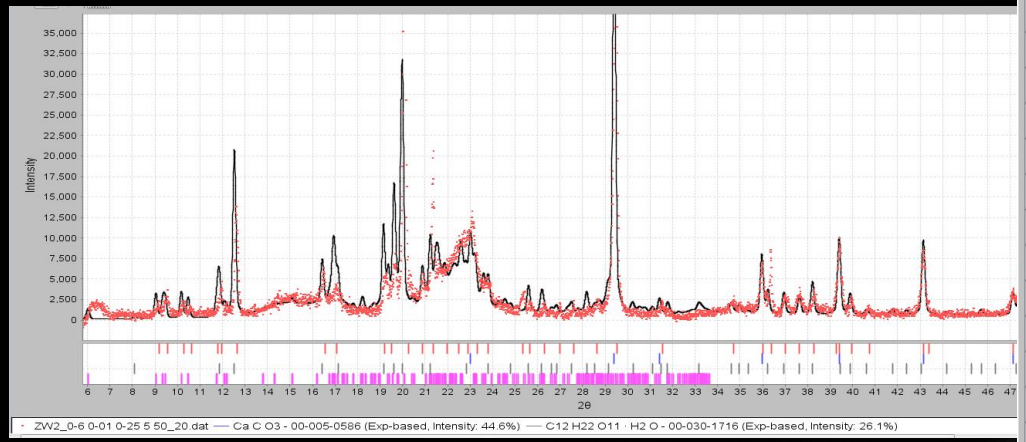
Pepcid AC

Famotidine Form I and Cellulose I β
2 phase simulation (black) vs
experimental



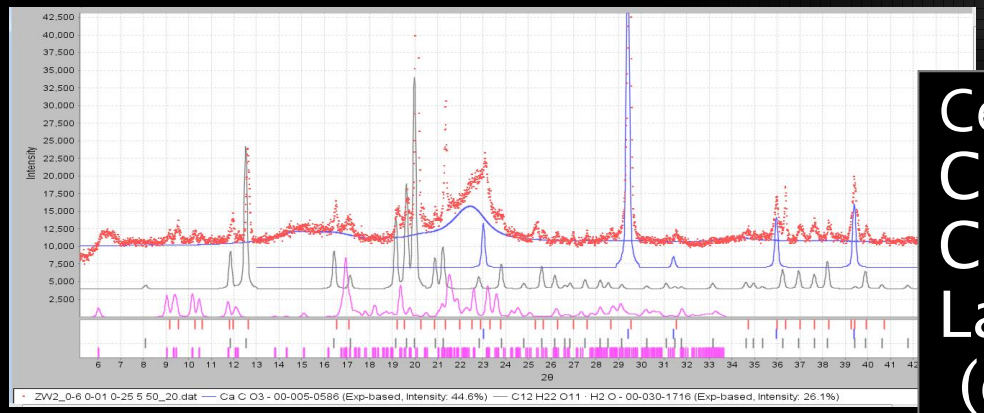
Lipitor
Using Pharmaceutical and Excipient subfile

Summed Phases



Ex d	Ex I	P1 d	P1 I	P2 d	P2 I	P3 d	P3 I
4.37651	100						
3.02128	41	3.035000	44			3.020400	1
4.15670	15			4.180000	9	4.181090	8
6.99331	12			7.060000	9		
3.87905	11	3.860000	5	3.893000	2		
3.94673	8					3.964080	1
1.87431	8	1.875000	7				
2.29242	8						
3.81276	7					3.824670	19
4.54396	7			4.520000	23	4.533160	0
2.28409	7	2.285000	8	2.283000	0		
2.09512	7	2.095000	8	2.099000	0		
2.46714	7						
2.08405	7						
1.86944	7			1.867000	0		
4.04027	6					4.055780	9
1.91382	6	1.913000	7				

4 Individual Phases



Cellulose I β – nanocrystalline
CaCO3
Ca Atorvastatin Trihydrate
Lactose Monohydrate
(oriented 100)

Lipitor

Identification done by using the pharmacuetical and excipient subfile combination

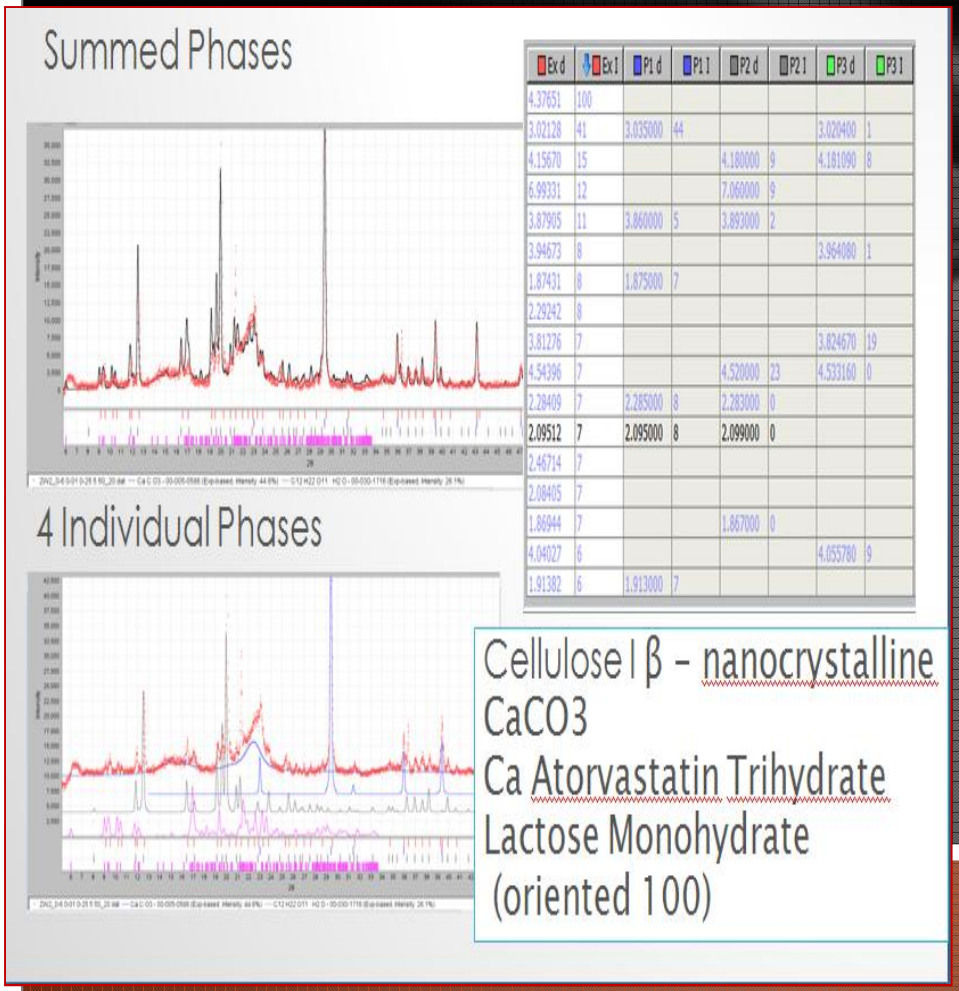
API – Atorvastatin reference patterns come from donations and patents

Microcrystalline cellulose identified by PD3 pattern PDF 00-060-1502

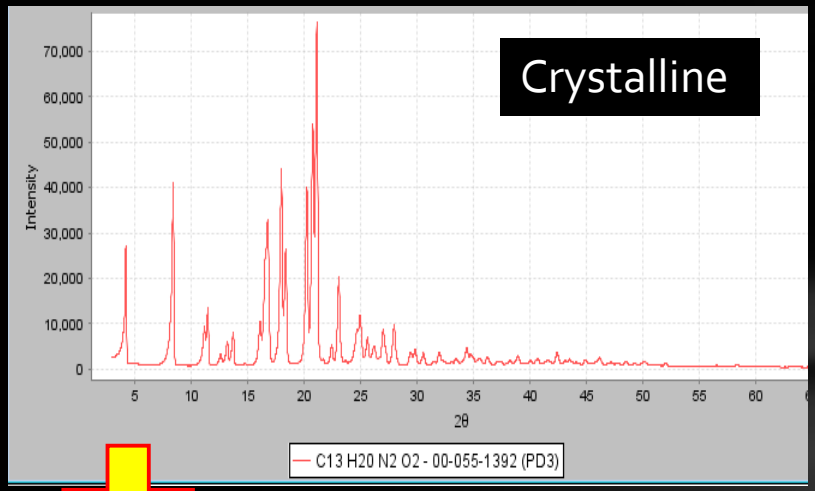
or

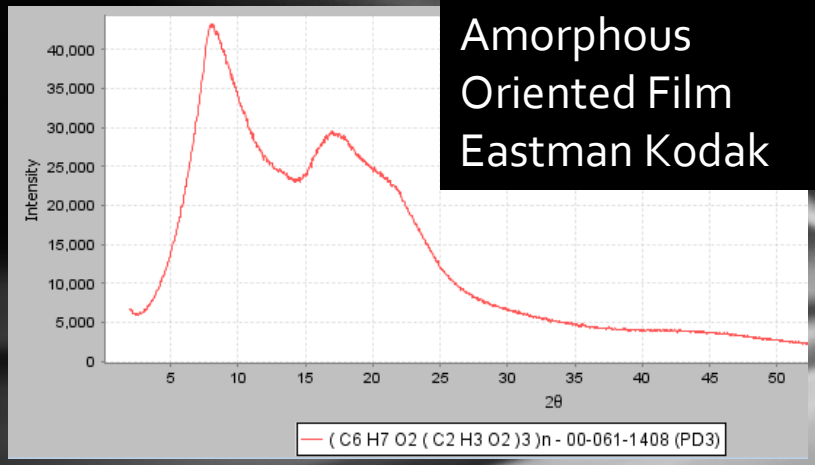
Use PDF 00-056-1718 Cellulose I β with a 35 Å crystallite simulation (Faber, Scardi, Leoni)

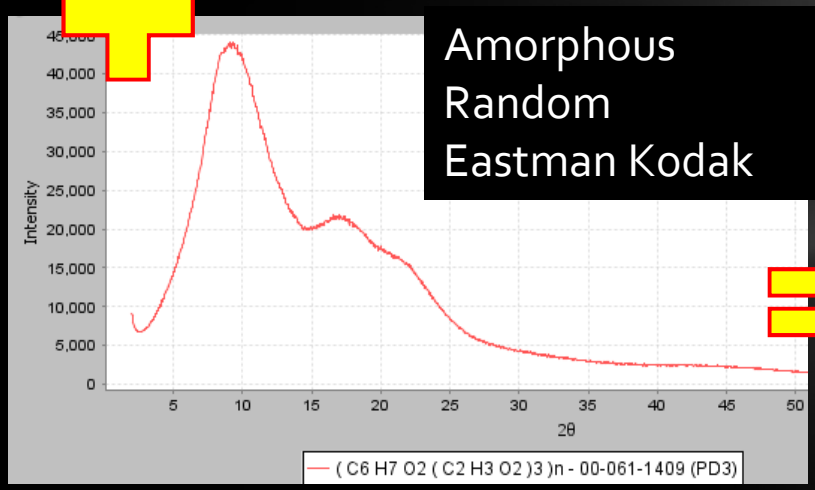
Lactose monohydrate oriented where we can identify the orientation (March-Dollase)

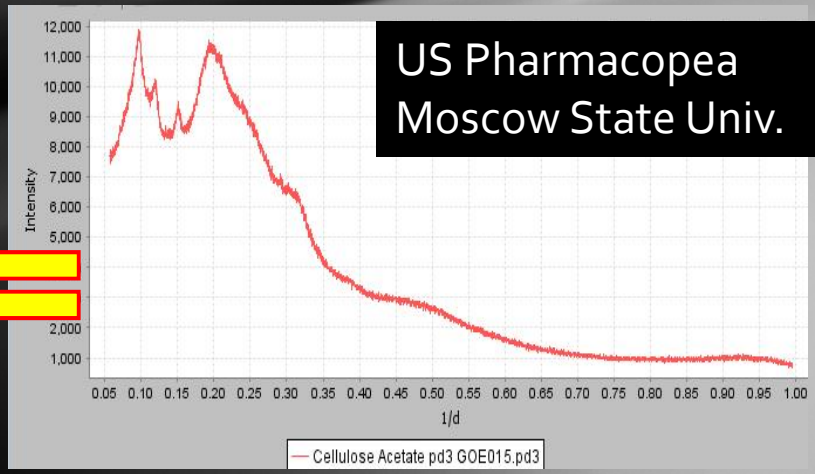


Cellulose Triacetate – Experimental Data

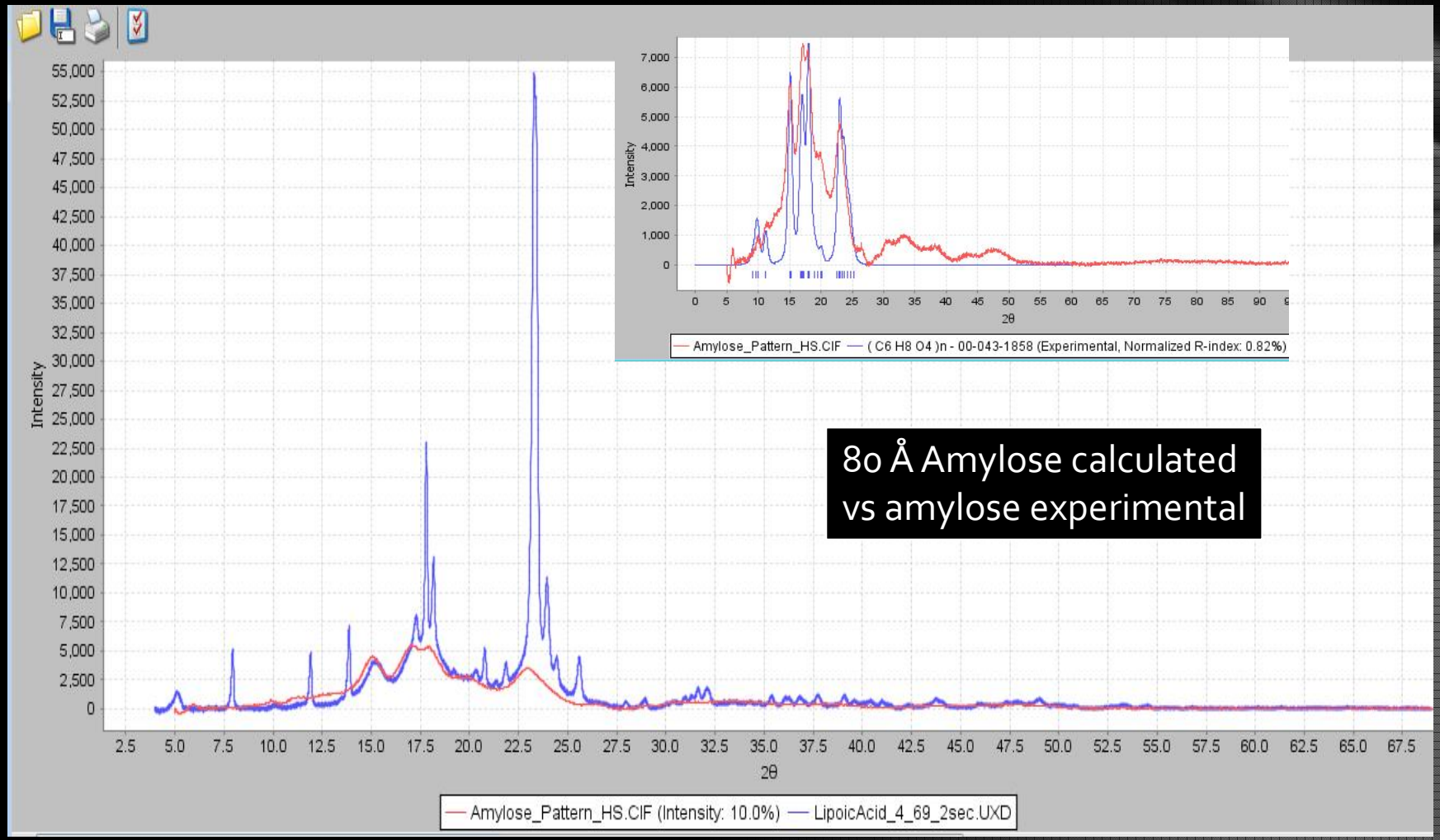




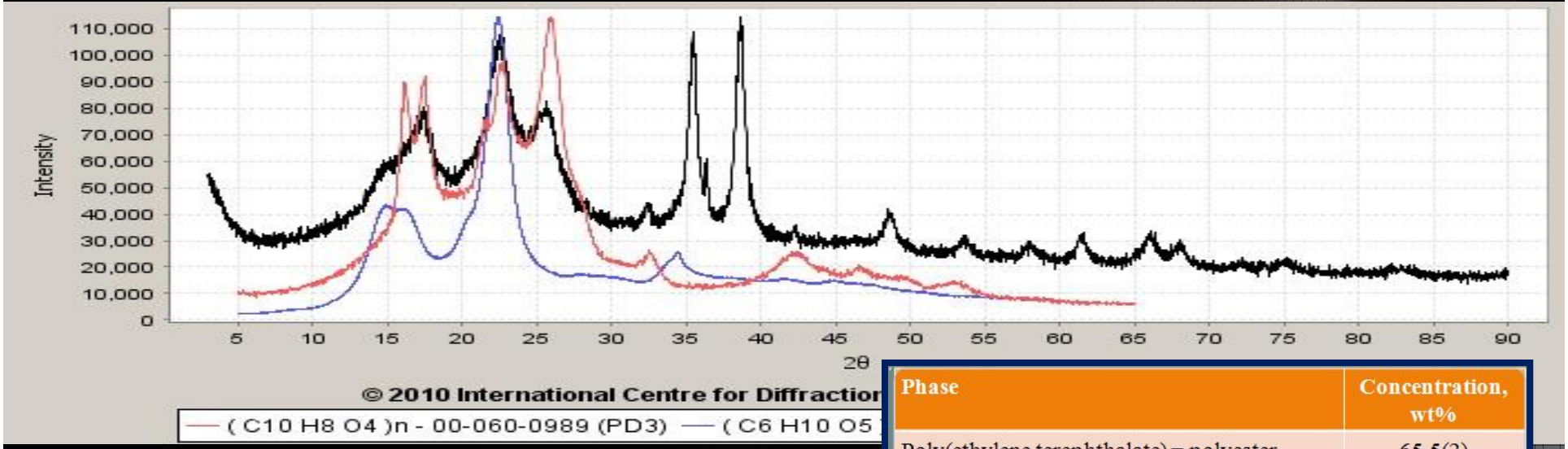




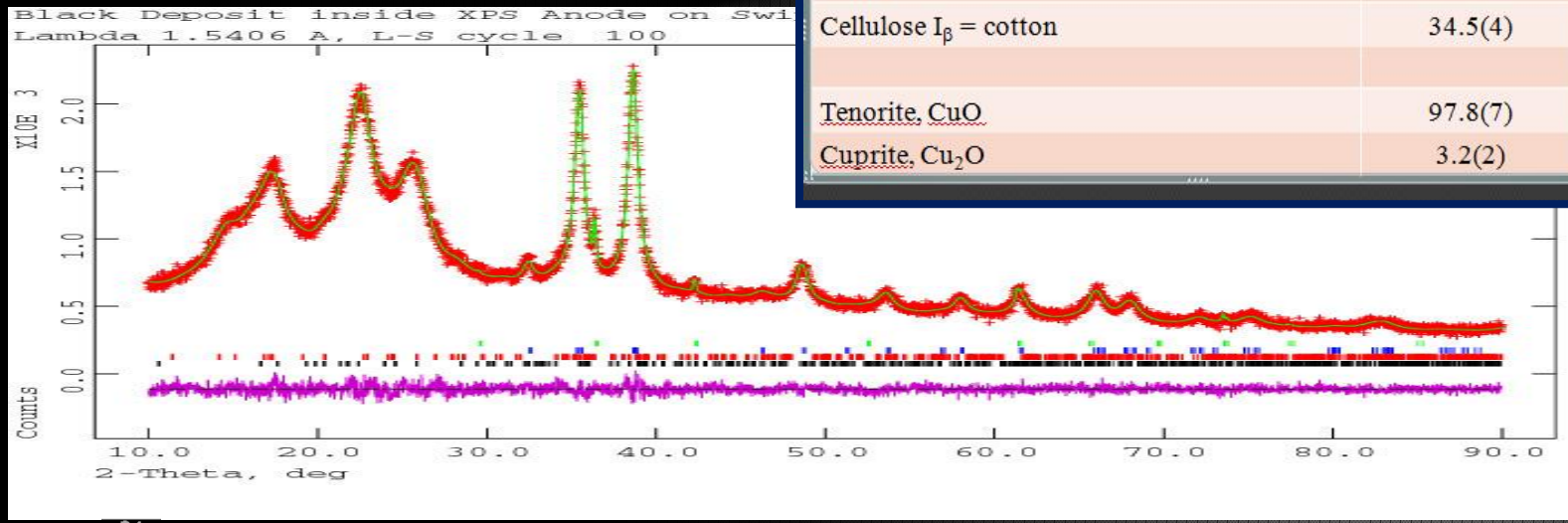
Amylose with Lipoic Acid



Digital Patterns – Total Pattern Analysis – modified Rietveld refinement



Phase	Concentration, wt%
Poly(ethylene terephthalate) = polyester	65.5(2)
Cellulose I_β = cotton	34.5(4)
Tenorite, CuO	97.8(7)
Cuprite, Cu_2O	3.2(2)



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 Apatitie	SEM 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 at different laboratories
Dextran	C, H, N analyses, TGA/DSC

Amorphous and nanomaterials

"Good Quality Mark"

– strong support data

PDF #	QM	Chemical Formula	Compound Name
00-060-1501	G	(C6 H10 O5)n	Cellulose, amorphous
00-062-1701	G	(C6 H7 O2 (O H)z · (C2 H3 O2)x...	Cellulose acetate butyrate
00-062-1702	G	(C6 H7 O2 (O H)z · (C2 H3 O2)x...	Cellulose acetate butyrate
00-062-1712	G	(C4 H8 O2)n · (C2 H4 O2)n	Cellulose acetate butyrate
00-062-1713	G	C164 H174 O111	Cellulose acetate
00-062-1714	G	C116 H116 O64	Cellulose acetate phthalate, amorph...
00-063-1501	G	H (C6 H10 O5)n O H	Dextran-4, amorphous
00-063-1502	G	(C6 H10 O5)n	Dextran-250, amorphous
00-063-1503	G	(C6 H9 N O)n	Povidone, amorphous
00-063-1504	G	(C6 H9 N O)n (C4 H6 O2)n	Copovidone, amorphous
00-063-1505	G	(C6 H9 N O)n	Crospovidone, amorphous
00-063-1508	G		Pepsin A
00-063-1509	G	((C8 H14 O2)0.88 · (C2 H4 O)0....	Poly(vinyl butyral), amorphous
00-063-1511	G	C15 H31 C O2 C30 H61	Beeswax

Marginal Quality Mark

PDF #	QM	Chemical Formula	Compound Name
00-060-1506	M	(C16 H14 O3)n	Polycarbonate, amorphous
00-060-1507	M	(C8 H8)n	Polystyrene, atactic
00-060-1508	M	(C15 H17 N)n	Acrylonitrile butadiene styrene, amor...
00-060-1509	M	(C10 H8 O4)n	Poly(ethylene terephthalate), amorp...
00-061-1408	M	(C6 H7 O2 (C2 H3 O2)3)n	Cellulose triacetate
00-061-1412	M	(C14 H10 O4)n	α-Poly(ethylene-2,6-naphthalate)
00-062-1288	M	C2.22 H4.22 O0.22	Ethylene vinyl acetate
00-062-1289	M	C2.36 H4.36 O0.36	Ethylene vinyl acetate
00-062-1290	M	(C8.45 H14.9 O5)n	Methyl cellulose, amorphous
00-062-1703	M	(C6 H7 O2 (O H)z · (C2 H3 O2)x...	Cellulose acetate butyrate
00-062-1704	M	(C6 H7 O2 (O H)z · (C2 H3 O2)x...	Cellulose actetate proprionate
00-062-1705	M	(C4 H8)n	Poly(butene-1)
00-062-1706	M	(O C H2)n	Poly(oxymethylene)
00-062-1707	M	(O C5 H6 Cl4)n	Poly (3,3-bis(chloromethyl)oxetane)
00-062-1708	M	(C4 H8 O)n	Poly(tetrahydrofuran)
00-062-1709	M	(C H2 C H ((C6 H4) C H3))n	Poly(o-vinyl toluene)
00-062-1710	M	(C H2 C Cl2)n	Poly(vinylidene chloride)
00-062-1711	M	(C H2 C H (C6 H5))n (C H2 C H ...	Poly(styrene-acrylic acid)
00-063-1506	M	(C6 H10 O5)n	Cellulose II, coated
00-063-1507	M	(C6 H10 O5)n	Cellulose II
00-063-1510	M	((C8 H14 O2)0.88 · (C2 H4 O)0....	Poly(vinyl butyral), amorphous

Applications

Nanomaterials

- Starch in Lipoic Acid
- Cellulose in Lipitor, Allegra, Centrum Multivitamins, Pepcid AC, Benzepril, Benedryl, Kroger Decongestant, Promethazine, Donnatal, Effexor
- Lactose Hydrate in CVS decongestant (note: many formulations have larger particle sizes of this phase)

Amorphous Materials

- Amorphous cellulose in most pharmacueticals with nanocellulose
- Povidone in Allegra

Conclusions

The Powder File uses experimental digital patterns and calculated digital patterns to study nanomaterials and amorphous materials

Using both calculation and experimental tools we can identify, quantitate, measure crystallinity and crystallite size.

To distinguish small crystallite (< 50 Å) nanomaterials from amorphous materials often requires additional supplementary information (crystal structures, PDF, SEM, DSC/TGA, NMR etc). This information is being added to the database and used to determine quality.

References and Acknowledgements

Petkov, V., Ren, Y., Kabekkodu, S., Murphy, D., **(2013)**, "Atomic Pair Distribution Functions analysis on low-Z materials of limited degree of structural coherence", an invited article to Physical Chemistry Chemical Physics, *accepted for publication 2013.*

T. G. Fawcett, C.E. Crowder, S. N. Kabekkodu, F. Needham, J. A. Kaduk, T. N. Blanton, V. Petkov, E. Bucher and R. Shpanchenko **(2013)**, "Reference Materials for the Study of Polymorphism and Crystallinity in Cellulosics", *Powder Diffraction, 28(1), pp 18-32.*

Jim Kaduk, Poly Crystallography Inc., – Amylose, Rietveld refinement

Tom Blanton, Eastman Kodak Co. – SAXS and XRD of nano-Ceria and nano Apatite from Cerion Corp, NMR data on substituted celluloses

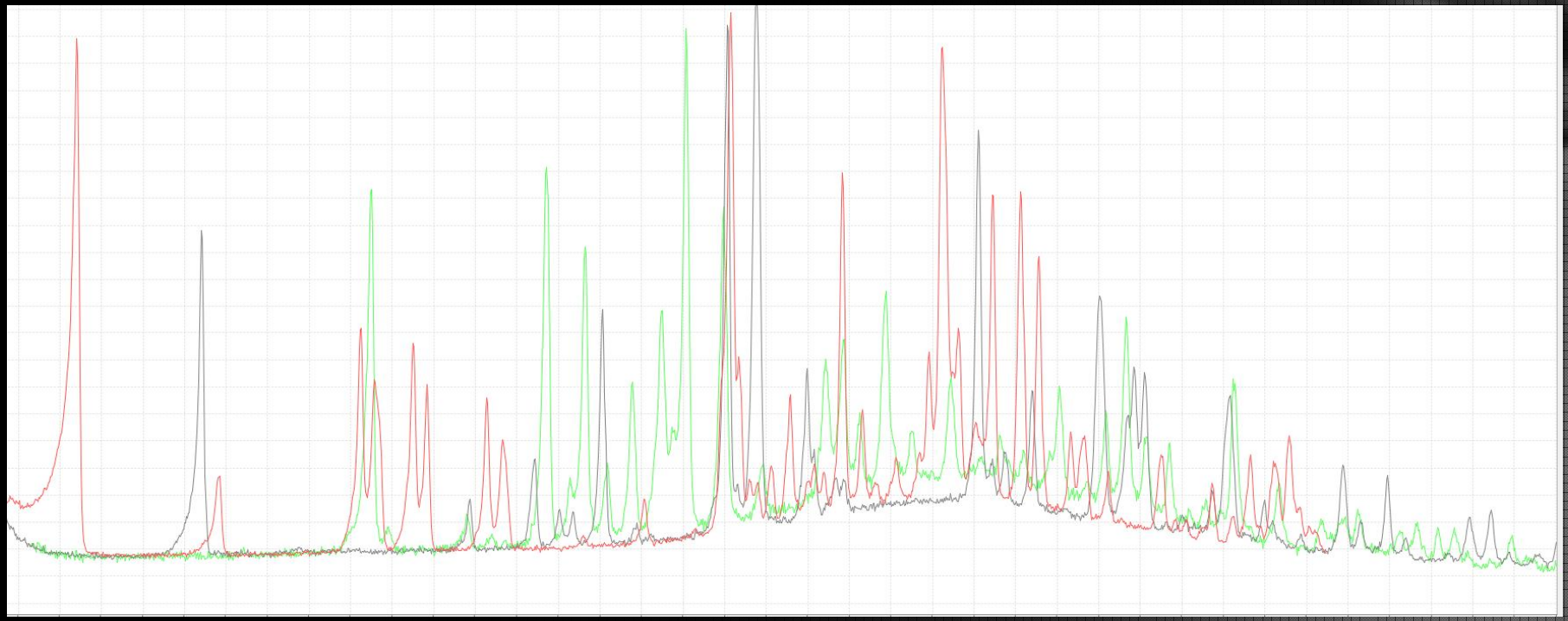
Ewa Bucher, International Paper – Cryogrinding studies of cellulose

Cam Hubbard (retired), Oak Ridge National Laboratory – pharmaceutical samples and data

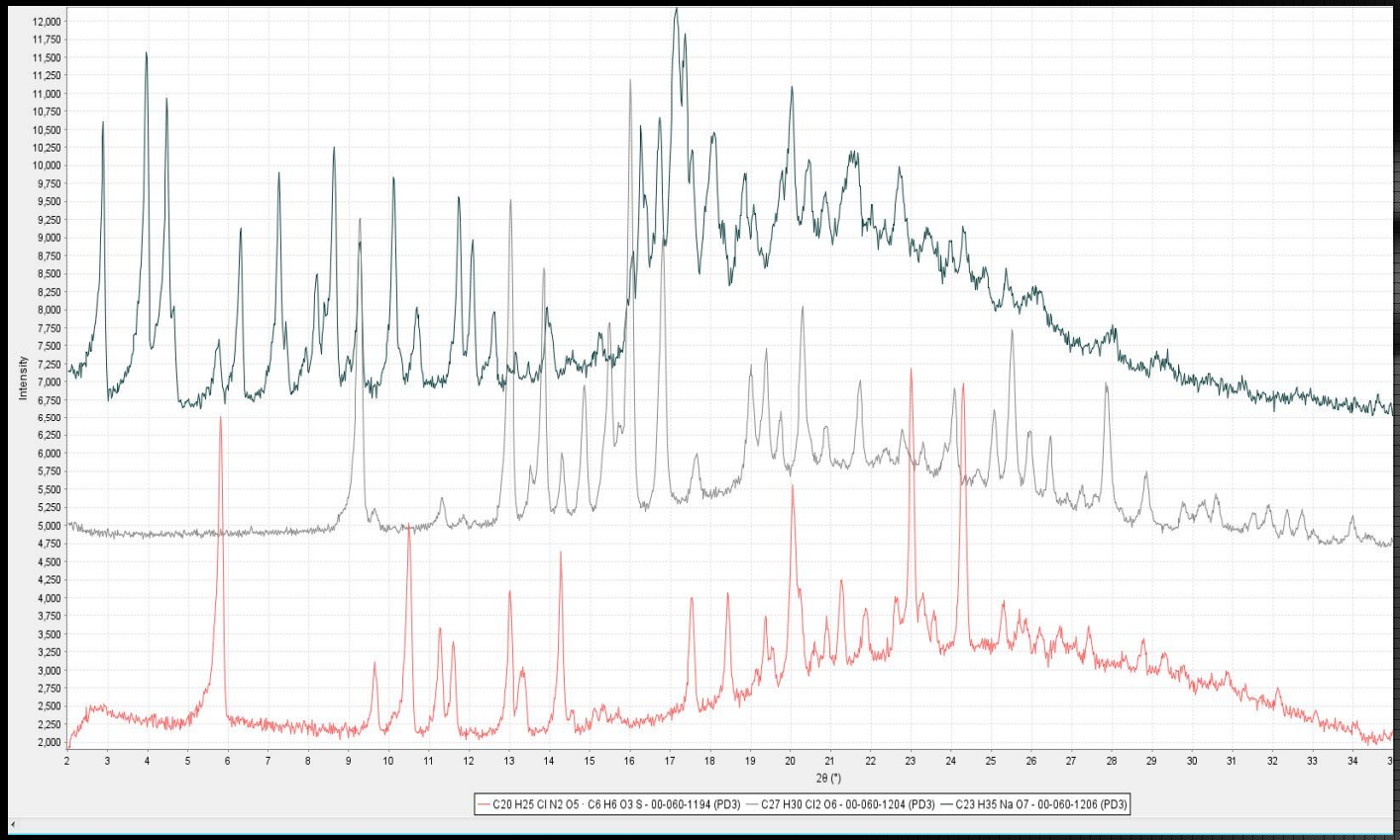
Offices of Nicholas Giuliani, MD – pharmaceutical samples

Capillary – Martin Vickers

The capillary is amorphous not the drug



Mixed Crystallinity Pharmaceuticals

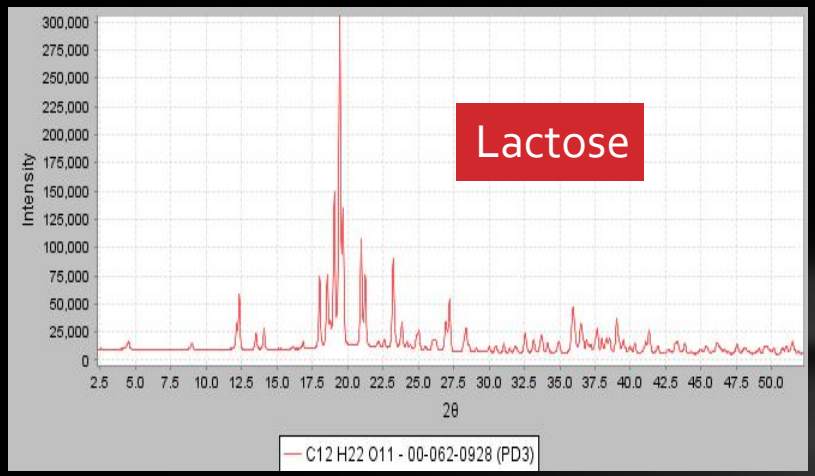


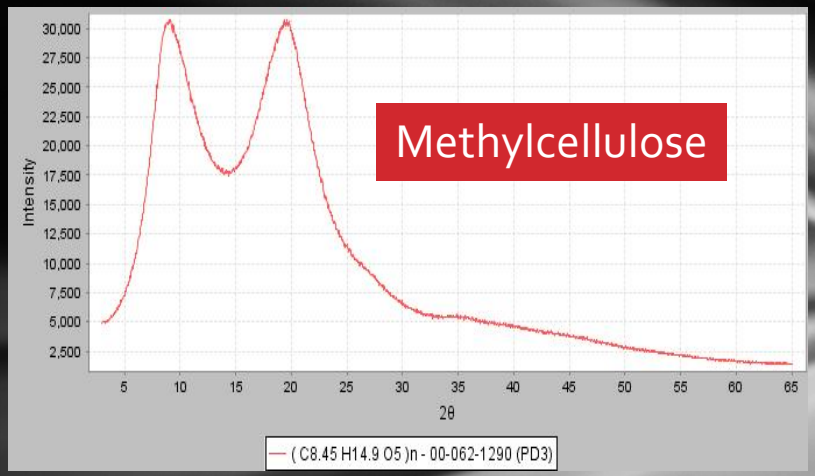
Na Provastatin

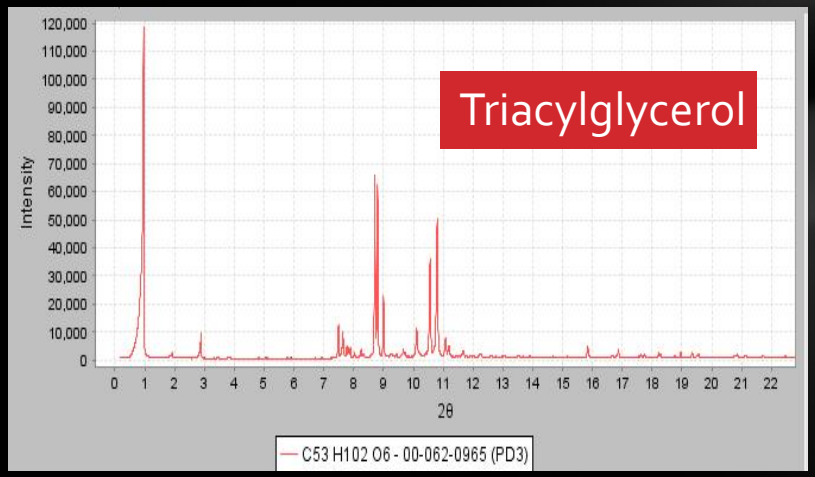
Mometasone

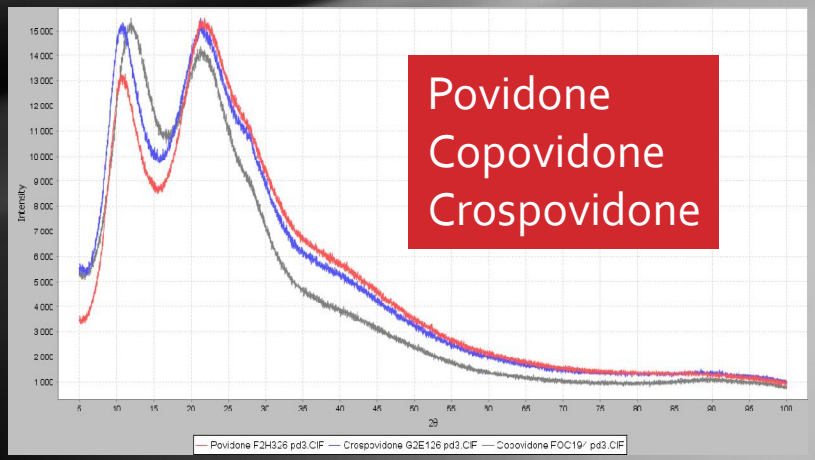
Amlodepine

Excipients

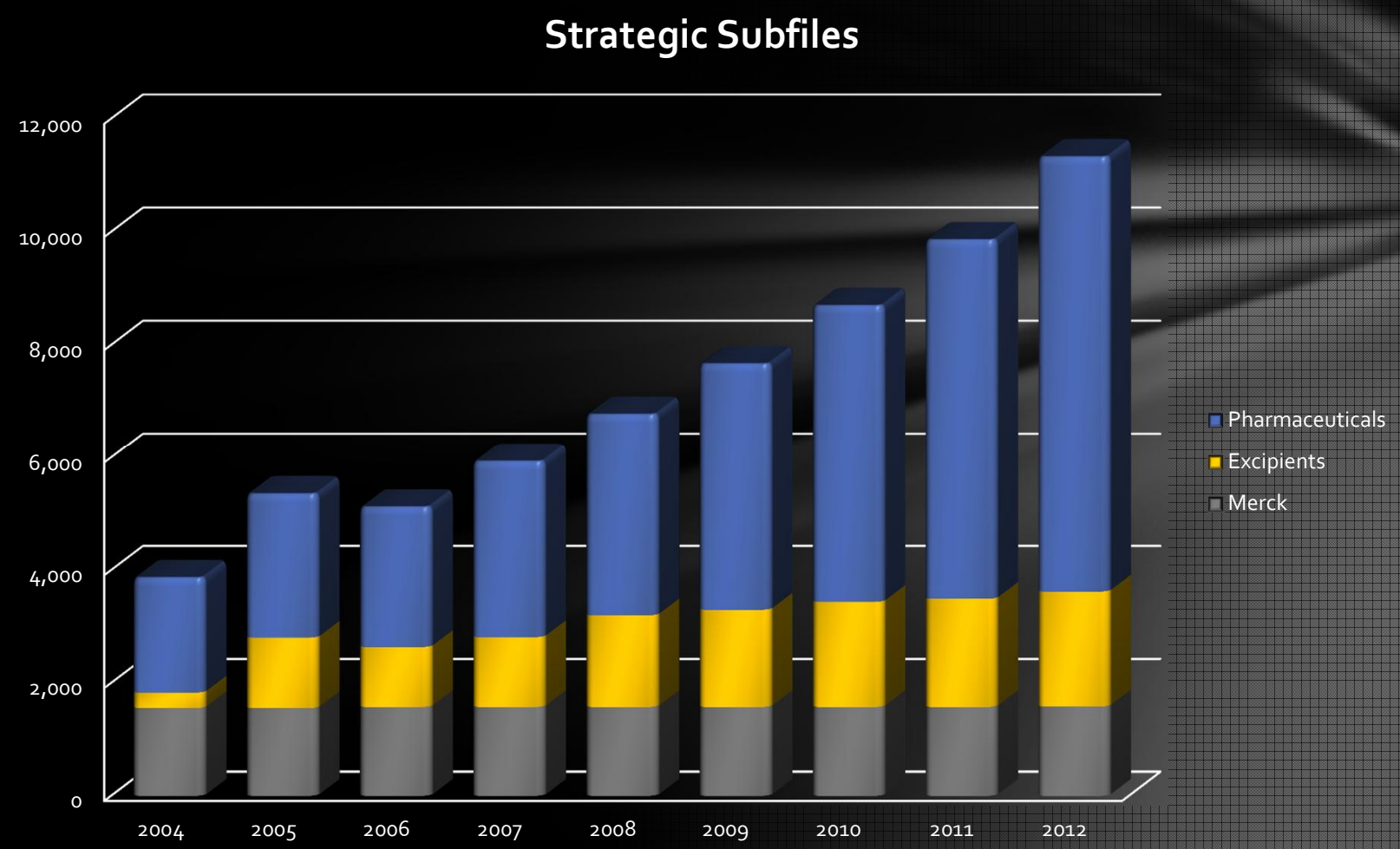

Lactose
Intensity
2θ
C12 H22 O11 - 00-062-0928 (PD3)


Methylcellulose
Intensity
2θ
(C8.45 H14.9 O5)n - 00-062-1290 (PD3)

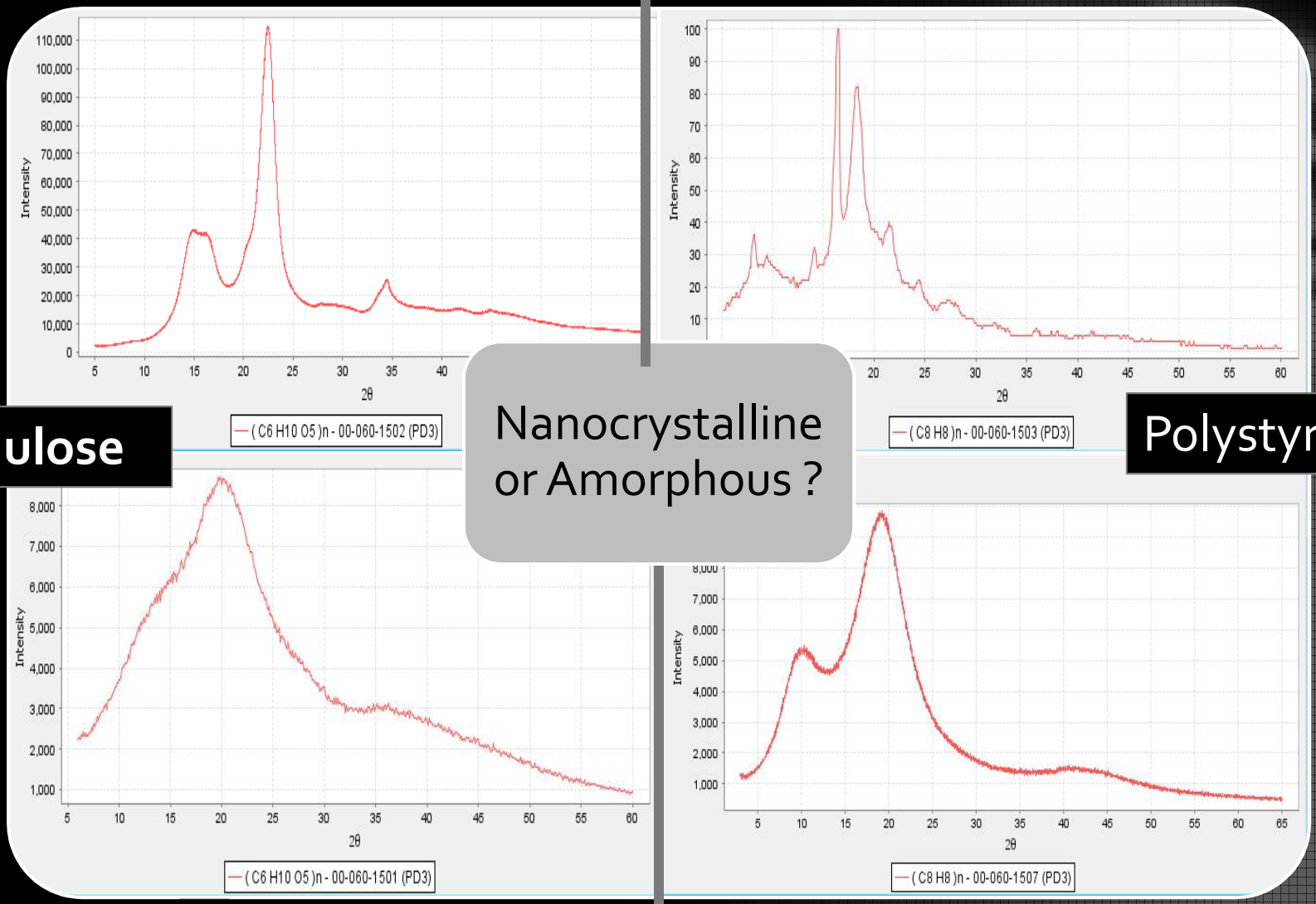

Triacylglycerol
Intensity
2θ
C53 H102 O6 - 00-062-0965 (PD3)


Povidone
Copovidone
Crospovidone
Intensity
2θ

Development of Strategic Subfiles



Experimental digital patterns

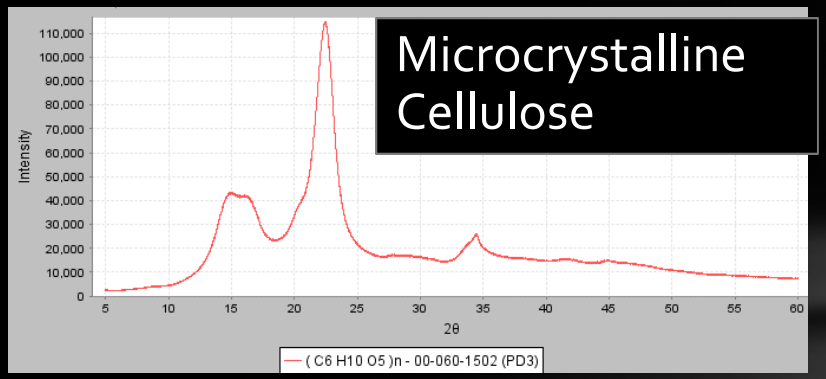


Cellulose

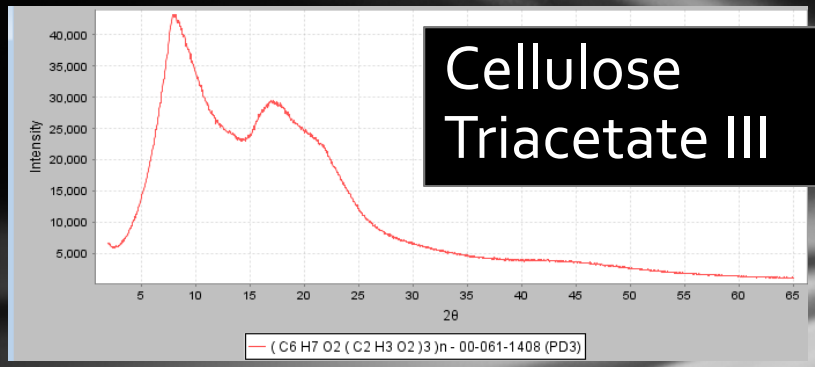
Nanocrystalline or Amorphous ?

Polystyrene

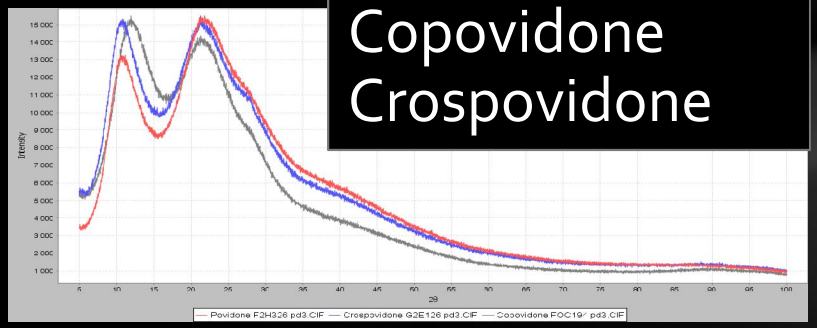
Polymeric excipients



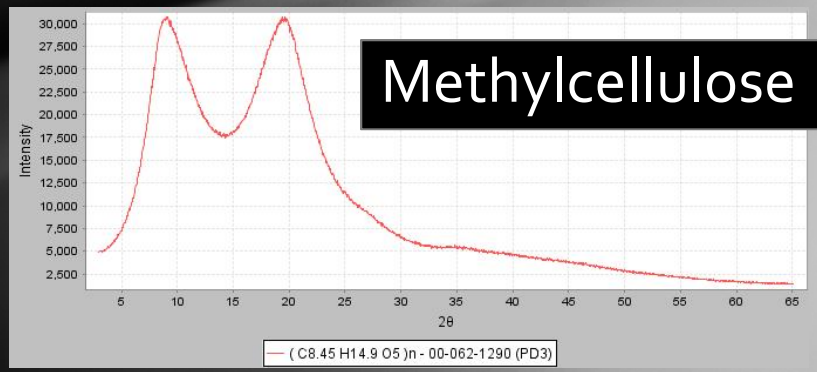
Microcrystalline Cellulose



Cellulose Triacetate III



Povidone
Copovidone
Crospovidone



Methylcellulose