Excipient Reference Data in the Powder Diffraction File (PDF®) for Phase Identification in Pharmaceutical Formulations

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Why have excipients in ICDD® databases?

The formulation of pharmaceutical drugs is a combinative process that incorporates a multitude of chemical constituents, which may be organic, inorganic, or polymeric in nature.

While the Active Pharmaceutical Ingredient (API) in a formulation is the key component that provides a drug its therapeutic functionality, excipients are generally the bulk of the content.

Due to the potential complexity of a diffraction pattern obtained from the analysis of a multiphase pharmaceutical drug, it is often necessary to analyze and identify all excipients before one can make an accurate identification of an API.

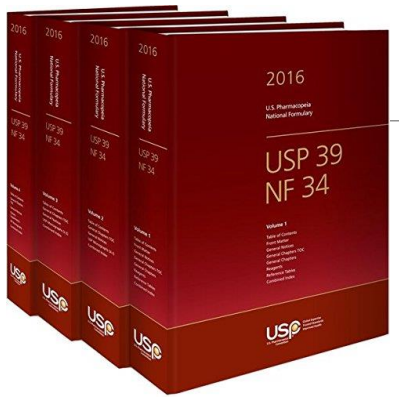
Currently, ICDD maintains an excipient subclass in the PDF that follows the list provided by the United States Pharmacopeia (USP). In PDF-4/Organics Release 2016, there are over 2,600 entries for excipient phases.

Excipients

Tablet and capsule formulations include

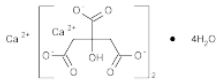
1. Diluents/fillers – increase the bulk content of the dosage form
2. Binders – promote cohesive compact during direct compression.
3. Disintegrants - breaks the dosage form into smaller particles when it comes in contact with a liquid
4. Lubricants - used to reduce the friction between the tablet and die cavity
5. Glidants - used to improve the flow property of the formulation
6. Coatings – applied to make swallowing easier, control release rate, extend storage life
7. Misc.
   - Flavorants - improve the flavor or give a pleasant taste to the formulation
   - Colorants - added to the formulation for visual appeasement and increase the patent compliance or for identification of the formulation
   - Adsorbants - used when there is an need to add a liquid or semisolid ingredient in the formulation

Excipient reference - USP-NF



The USP 39-NF 34 is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). It contains standards for medicines, dosage forms, drug substances, **excipients**, biologics, compounded preparations, medical devices, dietary supplements, and other therapeutics.

Calcium Citrate



$C_{12}H_{10}Ca_3O_{14} \cdot 4H_2O$ 570.49

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, calcium salt (2:3), tetrahydrate;

Calcium citrate (3:2), tetrahydrate [5785-44-4].

DEFINITION

Calcium Citrate contains four molecules of water of hydration. When dried at 150 ° to constant weight, it contains NL T 97.5% and NMT 100.5% of $Ca_3(C_6H_5O_7)_2$.

IDENTIFICATION

- **A.**

  Analysis: Dissolve 0.5 g in a mixture of 10 mL of water and 2.5 mL of 2 N nitric acid. Add 1 mL of mer curic sulfate TS, heat to boiling, and add 1 mL of potassium permanganate TS.

  Acceptance criteria: A white precipitate is formed.

- **B.**

  Sample: 0.5 g of Calcium Citrate

  Analysis: Ignite completely the *Sample* at as low a tempera- ture as possible, cool, and dissolve the residue in dilute gla- cial acetic acid (1:10). Filter, and add 10 mL of ammonium oxalate TS to the filtrate.

  Acceptance criteria: A voluminous white precipitate that is soluble in hydrochloric acid is formed.

ASSAY

- **PROCEDURE**

  Sample solution: Dissolve 350 mg of Calcium Citrate, previ- ously dried at 150 ° to constant weight, in 12 mL of 0.5 M hydrochloric acid, and dilute with water to about 100 mL, and 10 mL of 0.2 M edetate disodium. If necessar y, adjust with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 5.5. Transfer to a 100-mL volumetric flask, and dilute with water to volume. This solution contains 0.05 µg/mL of fluoride.

  Linearity solution B: Transfer 5.0 mL of the *Standard solu- tion* to a 250-mL plastic beaker, and proceed as directed for *Linearity solution A* beginning with "Add 50 mL of water,". This solution contains 0.25 µg/mL of fluoride.

  Linearity solution C: Transfer 10.0 mL of the *Standard solu- tion* to a 250-mL plastic beaker, and proceed as directed for *Linearity solution A* beginning with "Add 50 mL of water,". This solution contains 0.50 µg/mL of fluoride.

  Sample solution: Transfer 1.0 g of Calcium Citrate to a 100- mL beaker. Add 10 mL of water and, while stirring, 10 mL of 1 N hydrochloric acid. When dissolved, boil rapidly for 1 min, transfer the solution to a 250-mL plastic beaker, and cool in ice water. Add 15 mL of 1.0 M sodium citrate and 10 mL of 0.2 M edetate disodium, and adjust with 1 N so- dium hydroxide or 1 N hydrochloric acid to a pH of 5.5. Transfer this solution to a 100-mL volumetric flask, and di- lute with water to volume.

  Electrode system: Use a fluoride-specific, ion-indicating electrode and a silver–silver chloride reference electrode con- nected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* ⟨791⟩).

  Analysis

  Samples: *Linearity solution A, Linearity solution B, Linearity solution C,* and *Sample solution*

  Transfer 50 mL of each *Linearity solution A, Linearity solution B,* and *Linearity solution C* to separate 250-mL plastic beak- ers, and measure the potential of each solution with the *Electrode system.* Between each reading wash the elec- trodes with water, and absorb any residual water by blot- ting the electrodes dr y. Plot the logarithms of the fluoride concentrations (0.05, 0.25, and 0.50 µg/mL, respectively) versus potential to obtain a Standard response line.

  Transfer 50 mL of the *Sample solution* to a 250-mL plastic beaker, and measure the potential with the *Electrode sys- tem.* From the measured potential and the Standard re-

Excipient – XRD method reference

USP Global Expertise Trusted Standards Improved Health — USP–NF | Online

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A. X-Ray Diffraction (941)

Sample A: Add 2 g in small portions to 100 mL of water, with intense agitation. Allow to stand for 12 h to ensure complete hydration. Place 2 mL of the mixture so obtained on a suitable glass slide, and allow to air-dry at room temperature to produce an oriented film. Place the slide in a vacuum desiccator over a free surface of ethylene glycol. Evacuate the desiccator, and close the stopcock so that the ethylene glycol saturates the desiccator chamber. Allow to stand for 12 h.

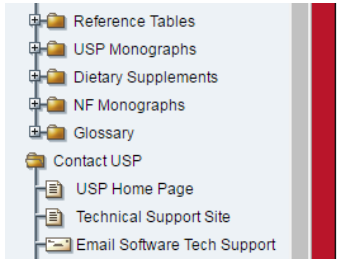
Sample B: Prepare a random powder specimen of Bentonite.

Analysis

Samples: *Sample A* and *Sample B*

Record the X-ray diffraction pattern of the samples, and determine the *d* values.

Acceptance criteria: The largest peak in the pattern of *Sample A* corresponds to a *d* value between 15.0 and 17.2 Å. The major peak in the region between 1.48 and 1.54 Å from the pattern of *Sample B* is between 1.492 and 1.504 Å.



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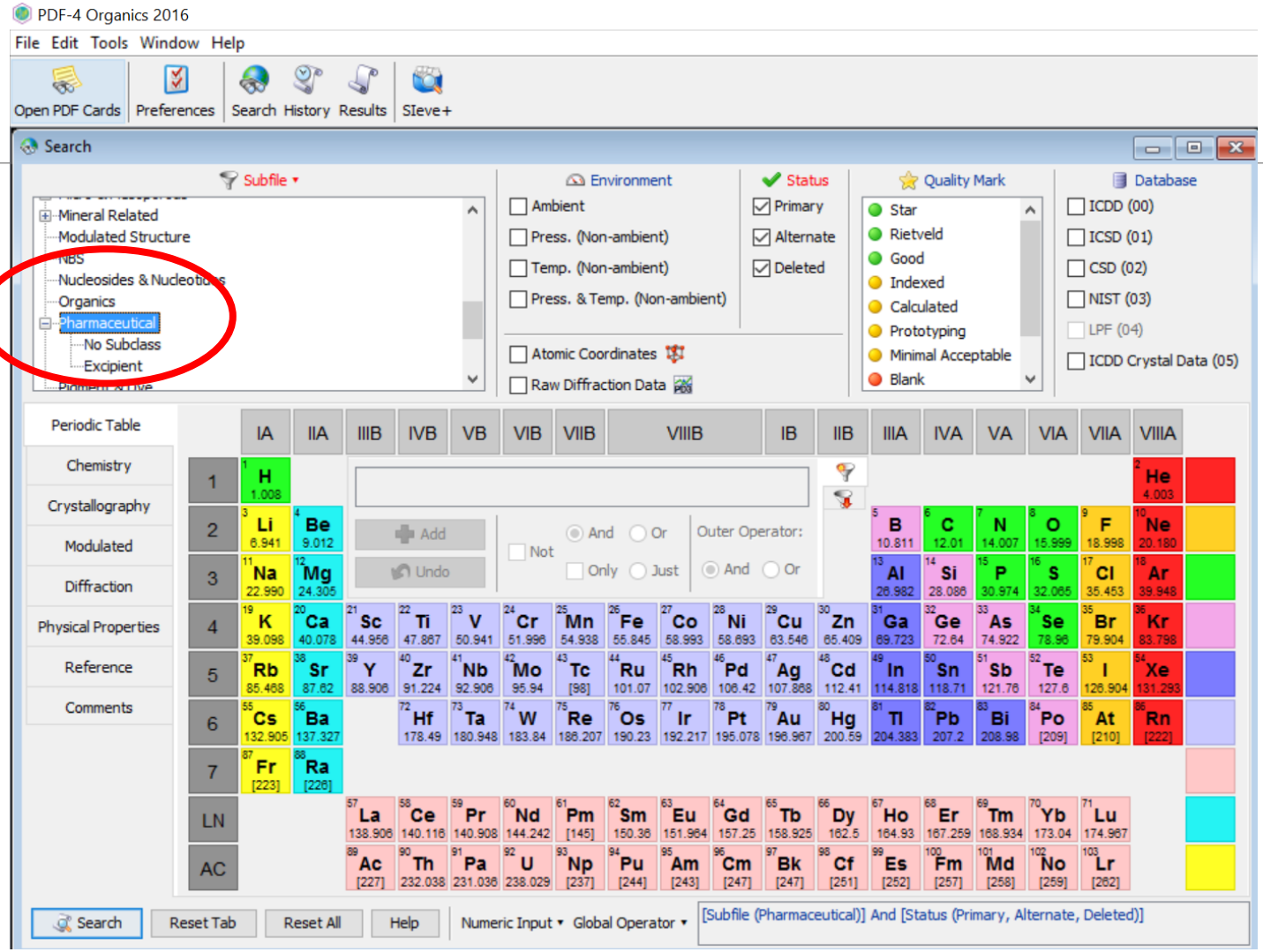
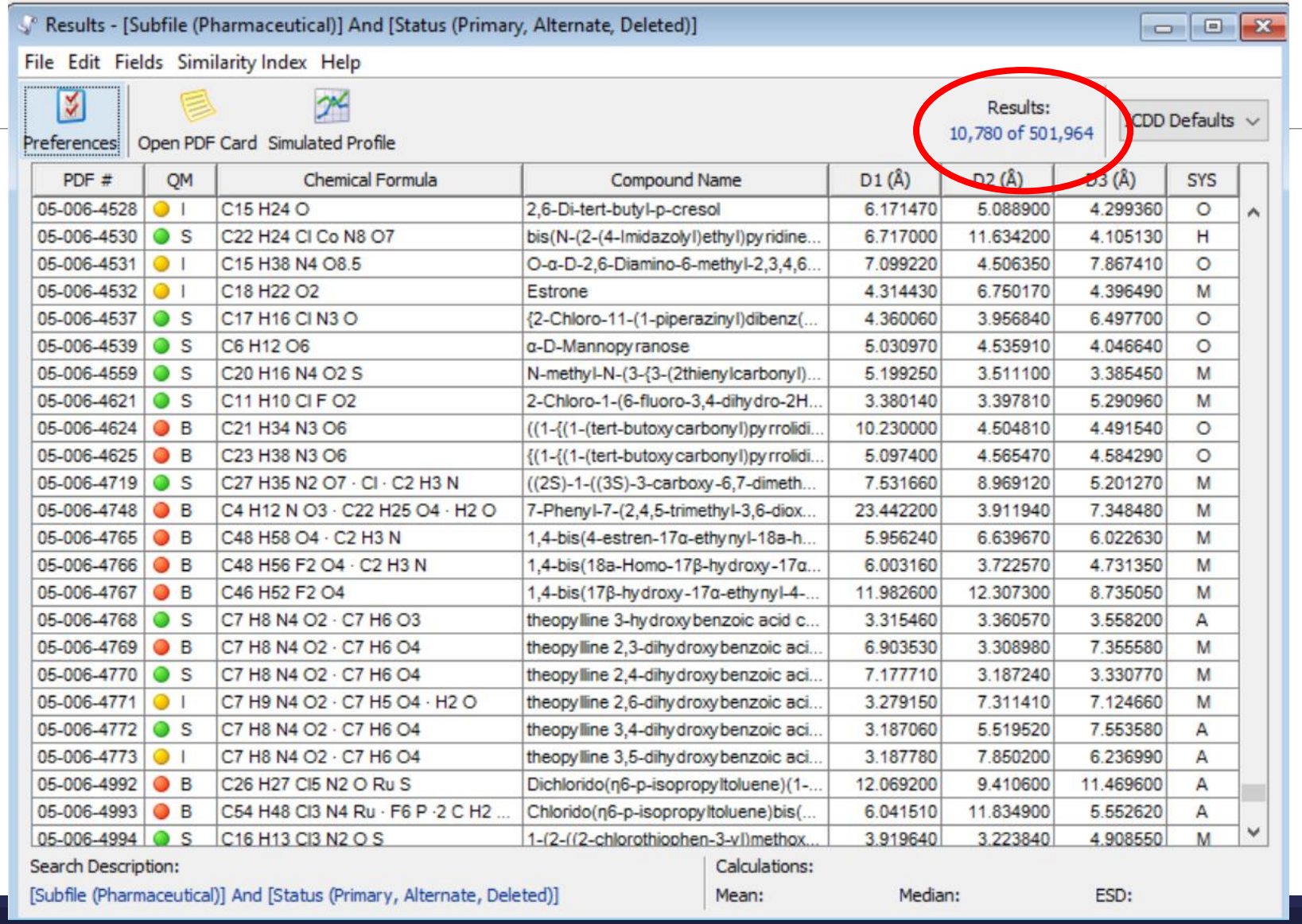
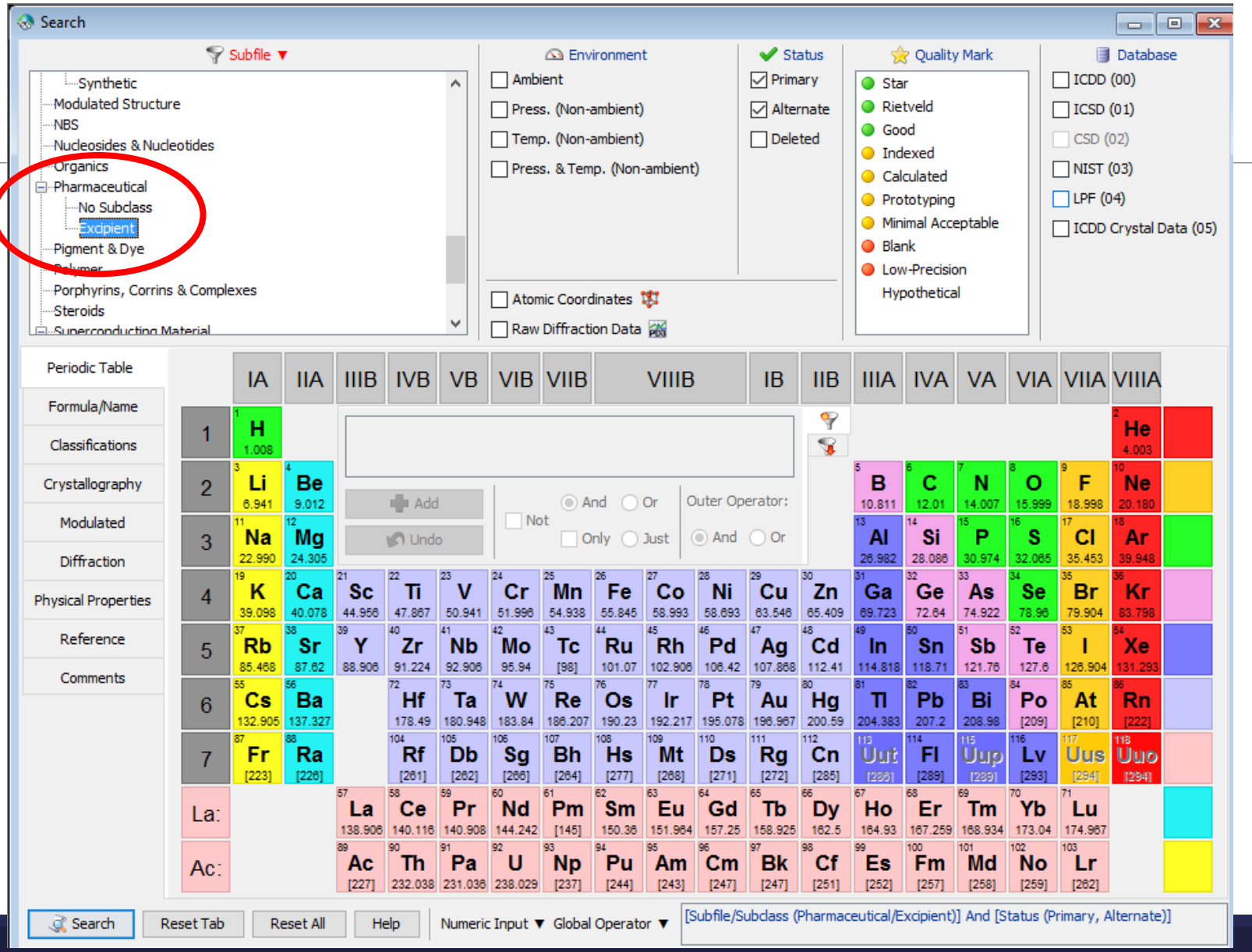
PDF-4/Organics database - pharmaceutical



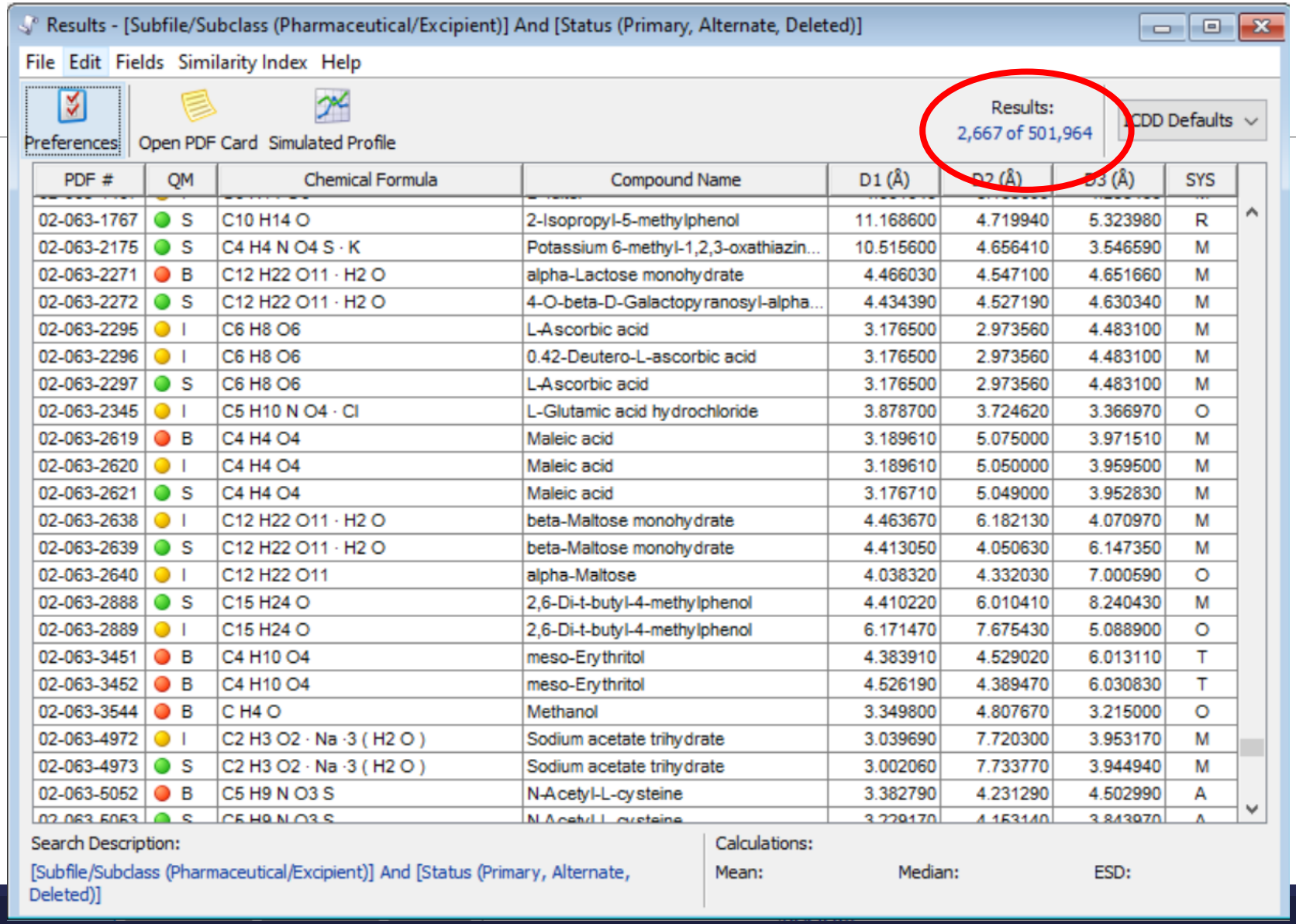
PDF-4/Organics database - pharmaceutical



PDF-4/Organics database - excipients

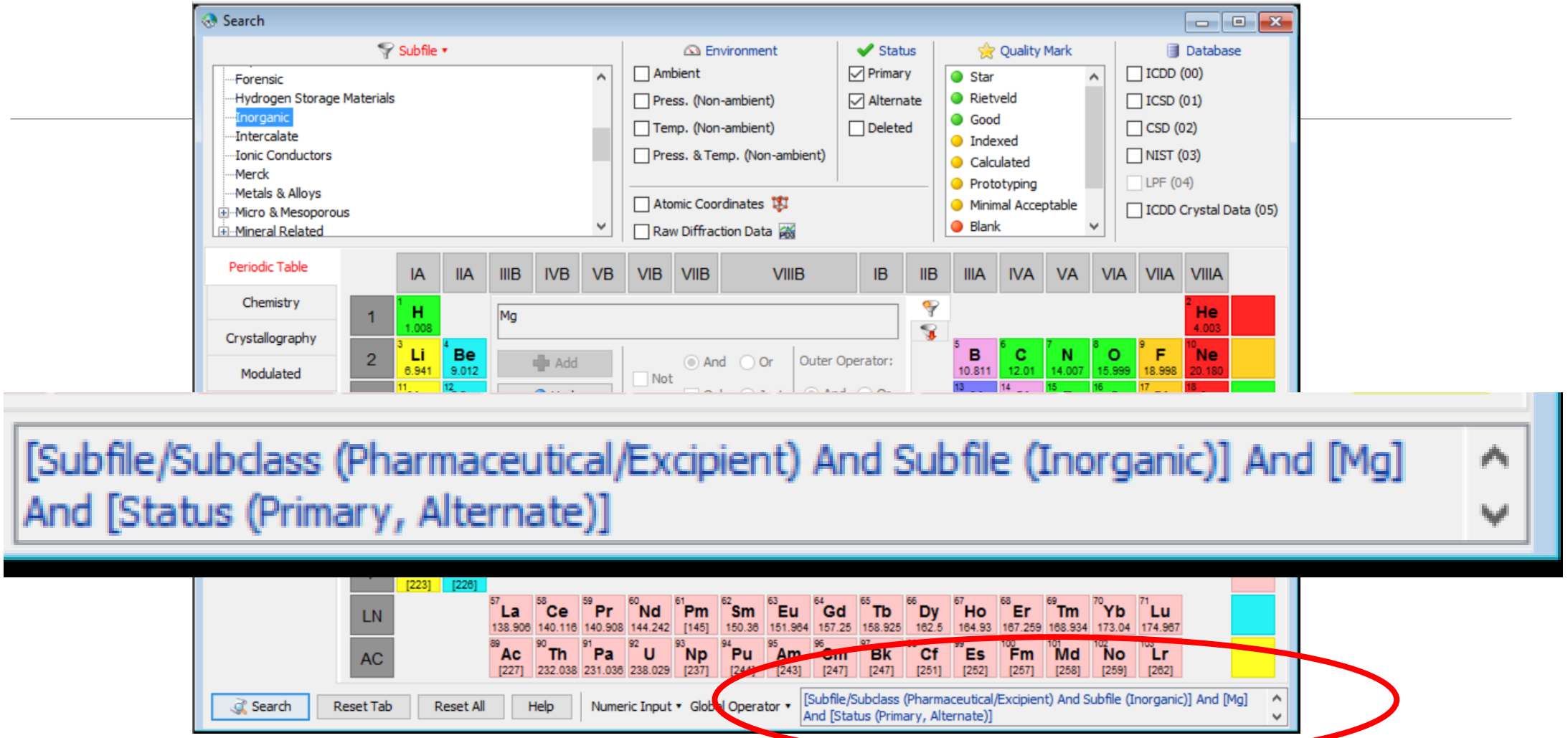


PDF-4/Organics database – excipients

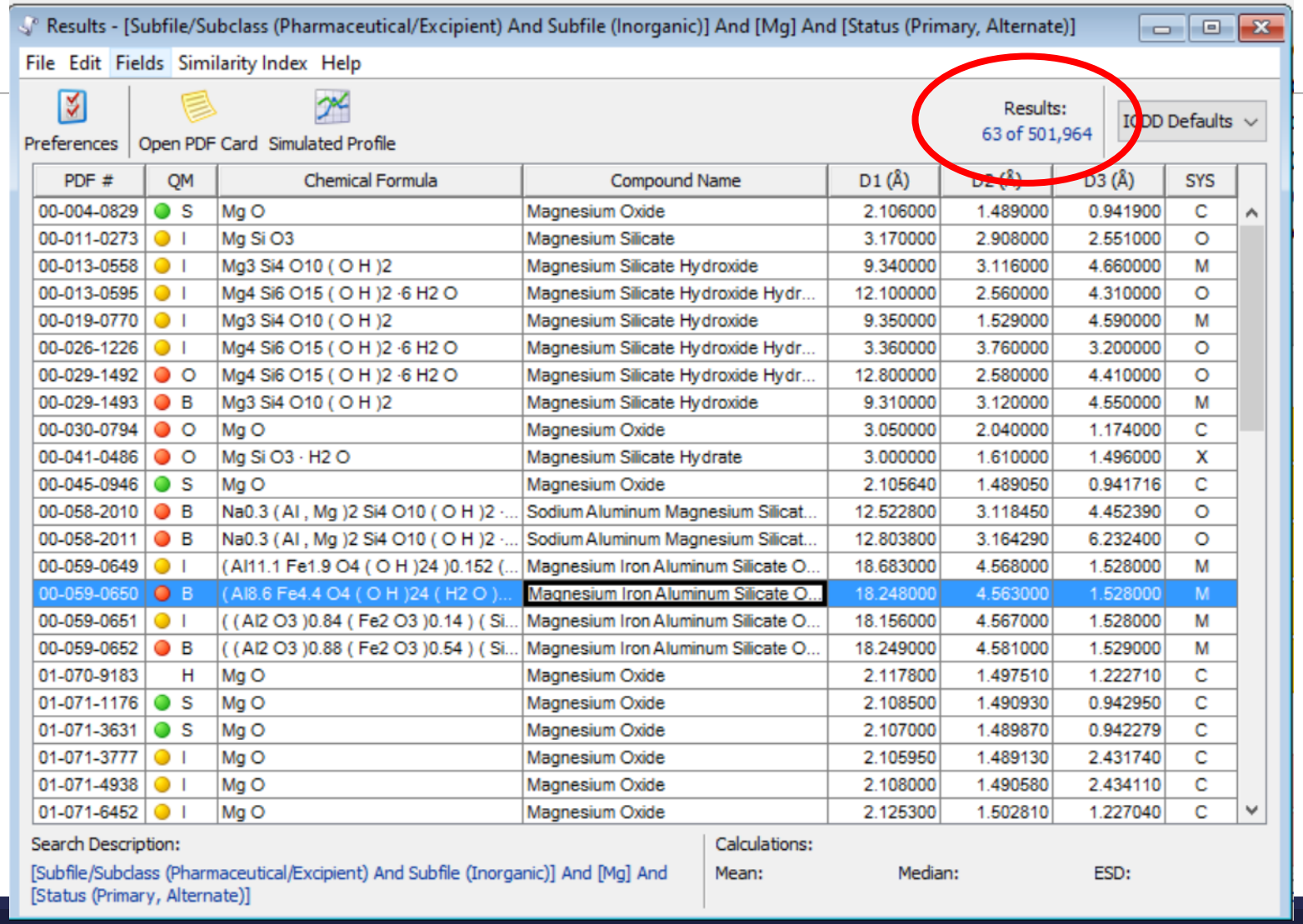


PDF #	QM	Chemical Formula	Compound Name	D1 (Å)	D2 (Å)	D3 (Å)	SYS
02-063-1767	S	C10 H14 O	2-Isopropyl-5-methylphenol	11.168600	4.719940	5.323980	R
02-063-2175	S	C4 H4 N O4 S · K	Potassium 6-methyl-1,2,3-oxathiazin...	10.515600	4.656410	3.546590	M
02-063-2271	B	C12 H22 O11 · H2 O	alpha-Lactose monohydrate	4.466030	4.547100	4.651660	M
02-063-2272	S	C12 H22 O11 · H2 O	4-O-beta-D-Galactopyranosyl-alpha...	4.434390	4.527190	4.630340	M
02-063-2295	I	C6 H8 O6	L-Ascorbic acid	3.176500	2.973560	4.483100	M
02-063-2296	I	C6 H8 O6	0.42-Deutero-L-ascorbic acid	3.176500	2.973560	4.483100	M
02-063-2297	S	C6 H8 O6	L-Ascorbic acid	3.176500	2.973560	4.483100	M
02-063-2345	I	C5 H10 N O4 · Cl	L-Glutamic acid hydrochloride	3.878700	3.724620	3.366970	O
02-063-2619	B	C4 H4 O4	Maleic acid	3.189610	5.075000	3.971510	M
02-063-2620	I	C4 H4 O4	Maleic acid	3.189610	5.050000	3.959500	M
02-063-2621	S	C4 H4 O4	Maleic acid	3.176710	5.049000	3.952830	M
02-063-2638	I	C12 H22 O11 · H2 O	beta-Maltose monohydrate	4.463670	6.182130	4.070970	M
02-063-2639	S	C12 H22 O11 · H2 O	beta-Maltose monohydrate	4.413050	4.050630	6.147350	M
02-063-2640	I	C12 H22 O11	alpha-Maltose	4.038320	4.332030	7.000590	O
02-063-2888	S	C15 H24 O	2,6-Di-t-butyl-4-methylphenol	4.410220	6.010410	8.240430	M
02-063-2889	I	C15 H24 O	2,6-Di-t-butyl-4-methylphenol	6.171470	7.675430	5.088900	O
02-063-3451	B	C4 H10 O4	meso-Erythritol	4.383910	4.529020	6.013110	T
02-063-3452	B	C4 H10 O4	meso-Erythritol	4.526190	4.389470	6.030830	T
02-063-3544	B	C H4 O	Methanol	3.349800	4.807670	3.215000	O
02-063-4972	I	C2 H3 O2 · Na · 3 (H2 O)	Sodium acetate trihydrate	3.039690	7.720300	3.953170	M
02-063-4973	S	C2 H3 O2 · Na · 3 (H2 O)	Sodium acetate trihydrate	3.002060	7.733770	3.944940	M
02-063-5052	B	C5 H9 N O3 S	N-Acetyl-L-cysteine	3.382790	4.231290	4.502990	A

PDF-4/Organics database – excipients – data mining

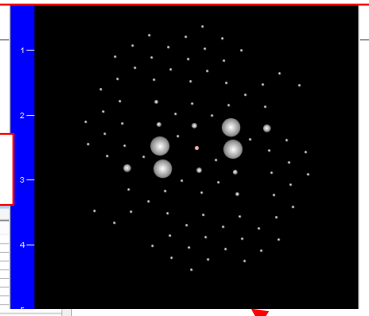


PDF-4/Organics database – excipients – data mining

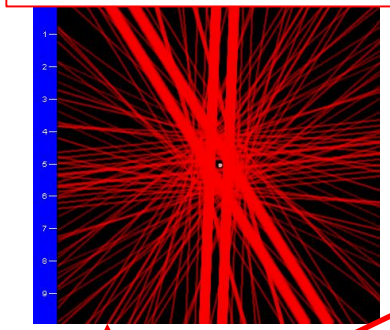


PDF entries with atomic coordinates

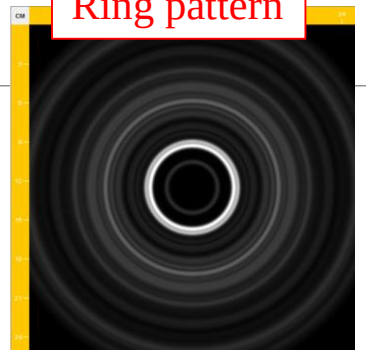
Electron diffraction pattern



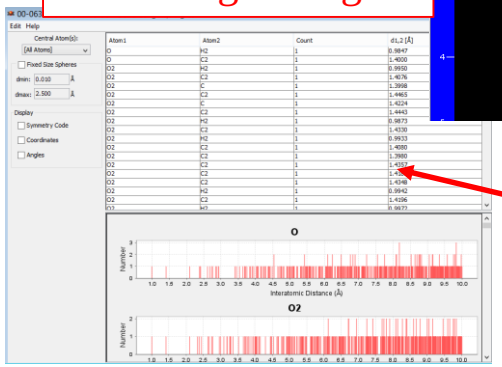
Electron backscatter pattern

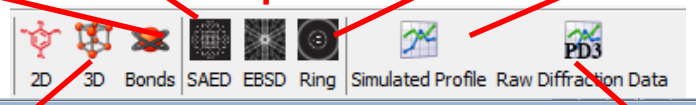


Ring pattern

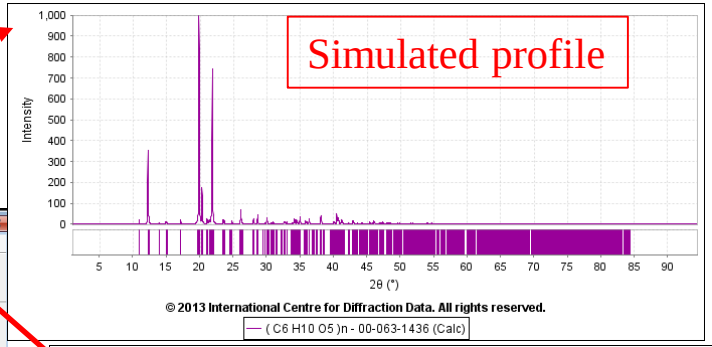


Bond lengths/angles

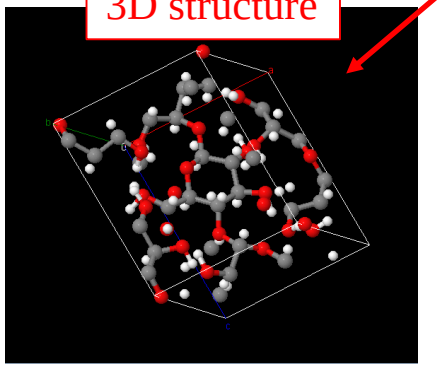


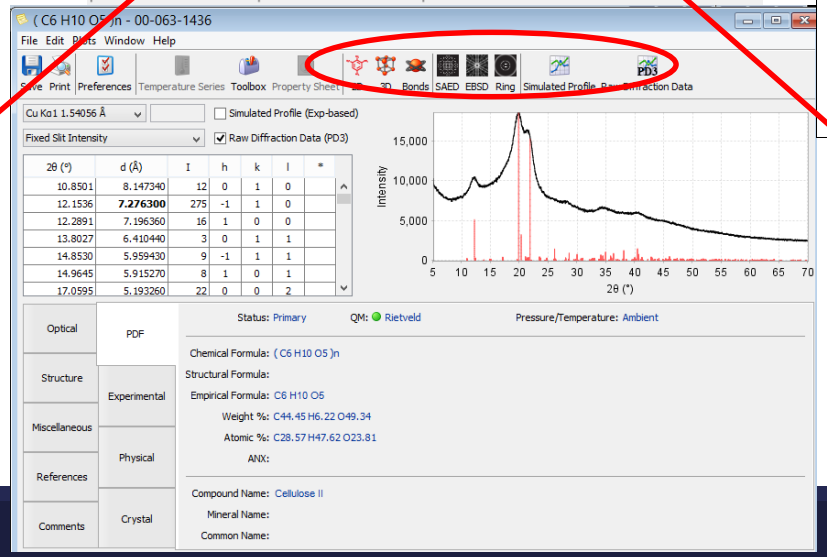


Simulated profile

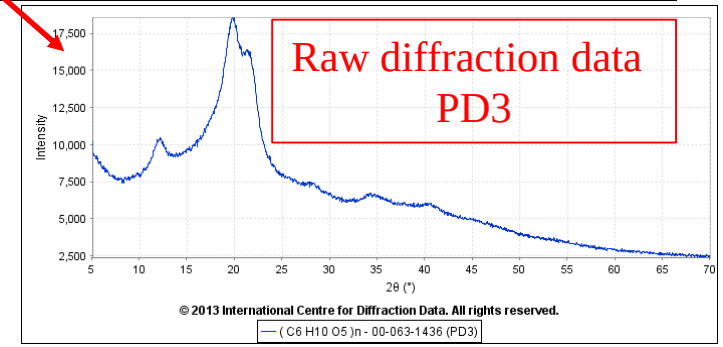


3D structure

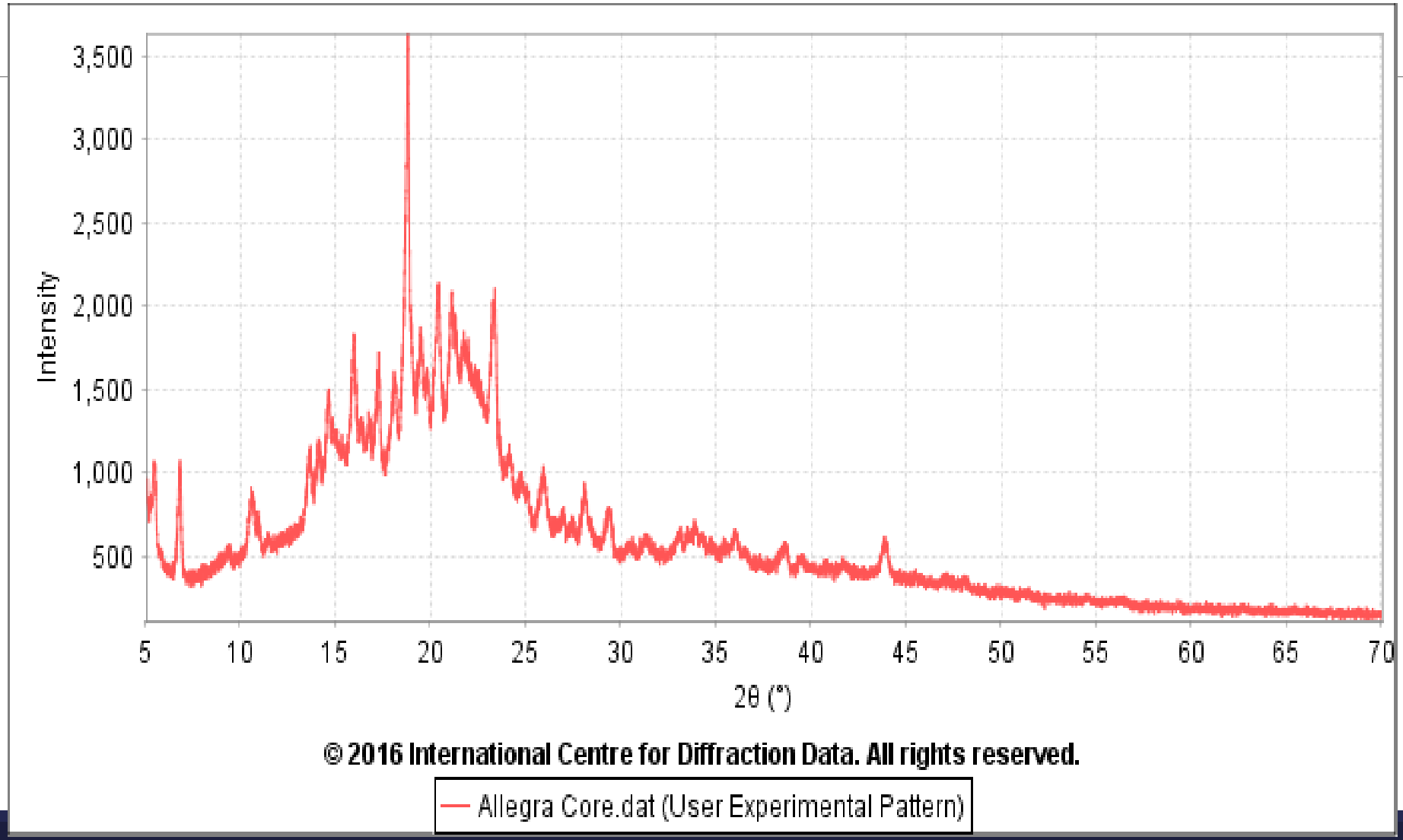




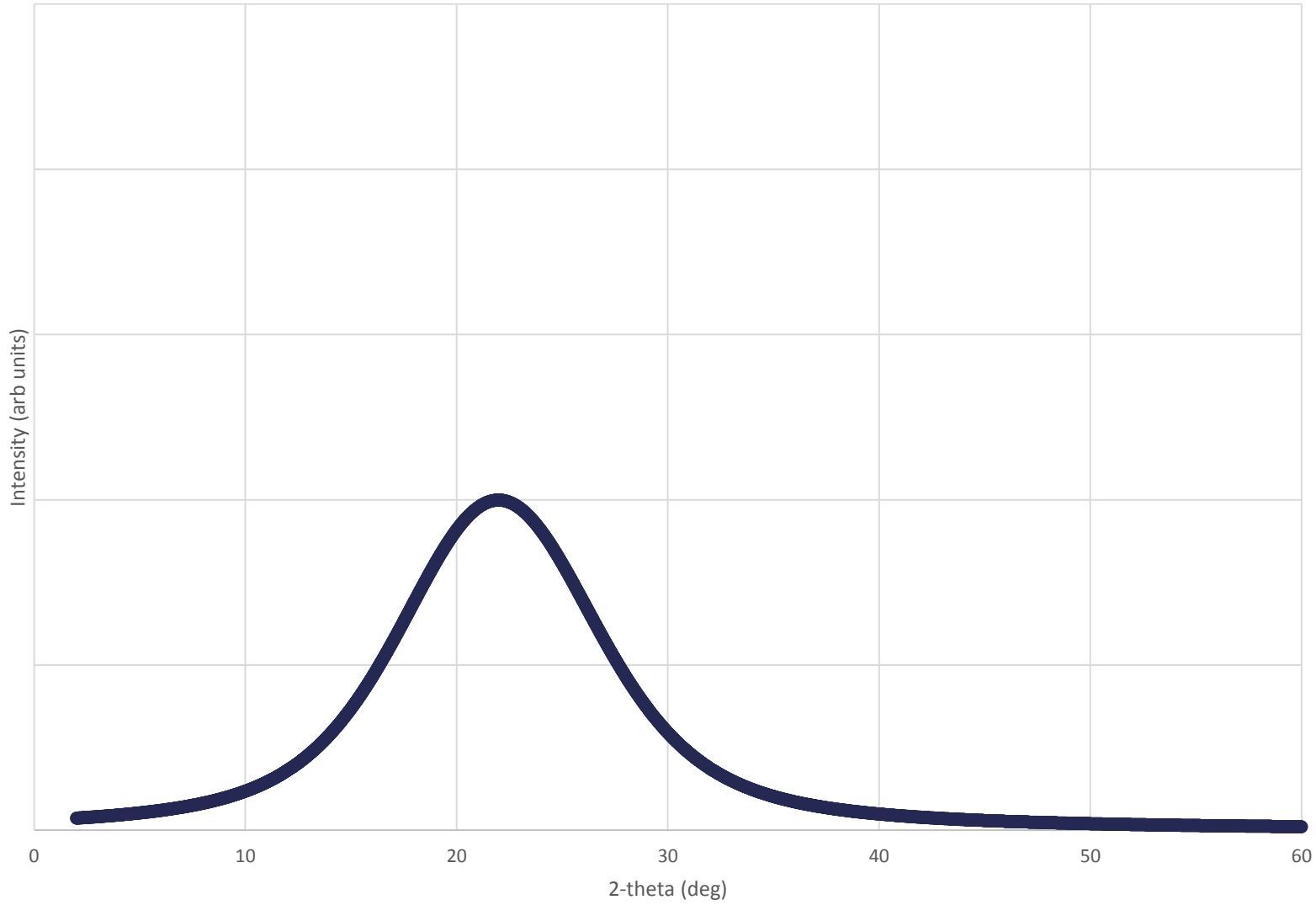
Raw diffraction data PD3



XRD pattern of Allegra®, antihistamine

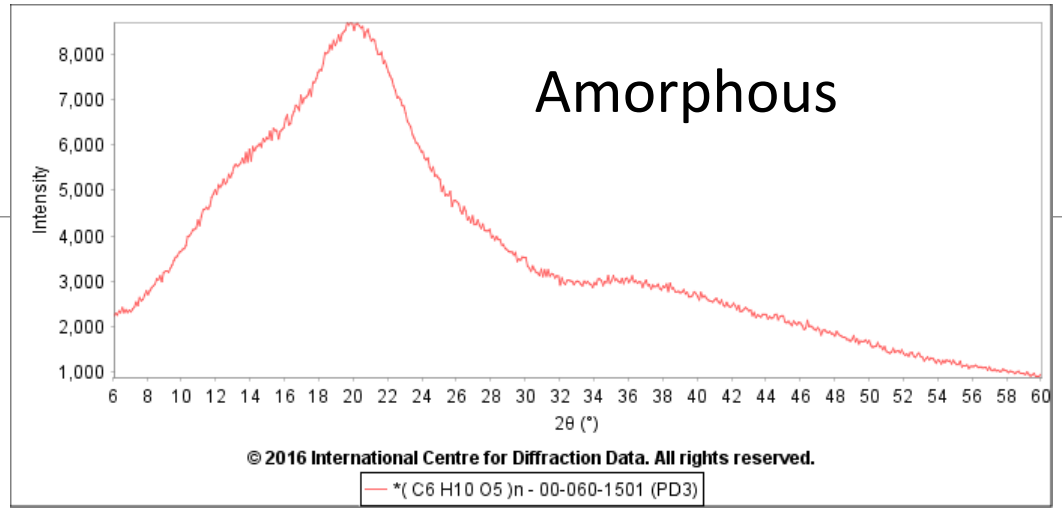


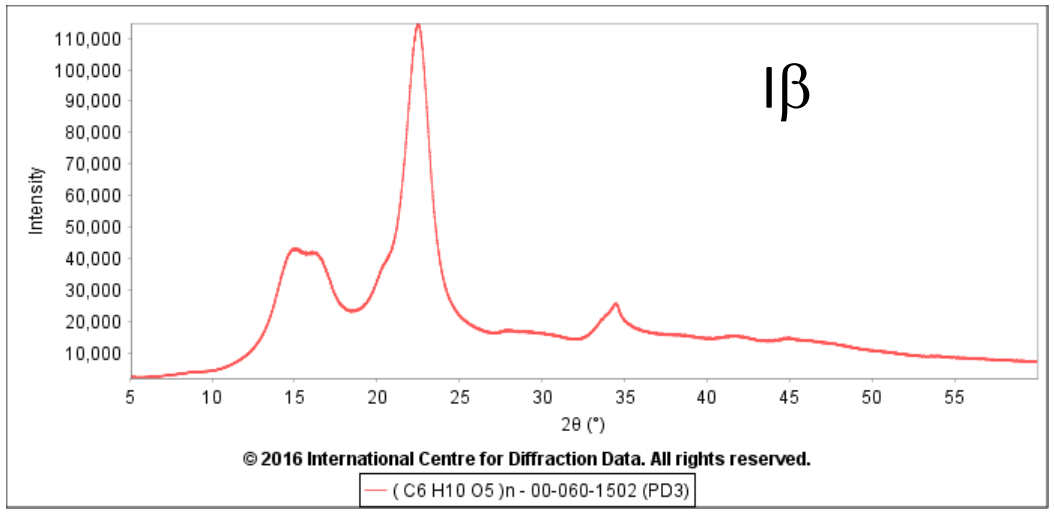
Can I just model the polymer amorphous component as a single peak?

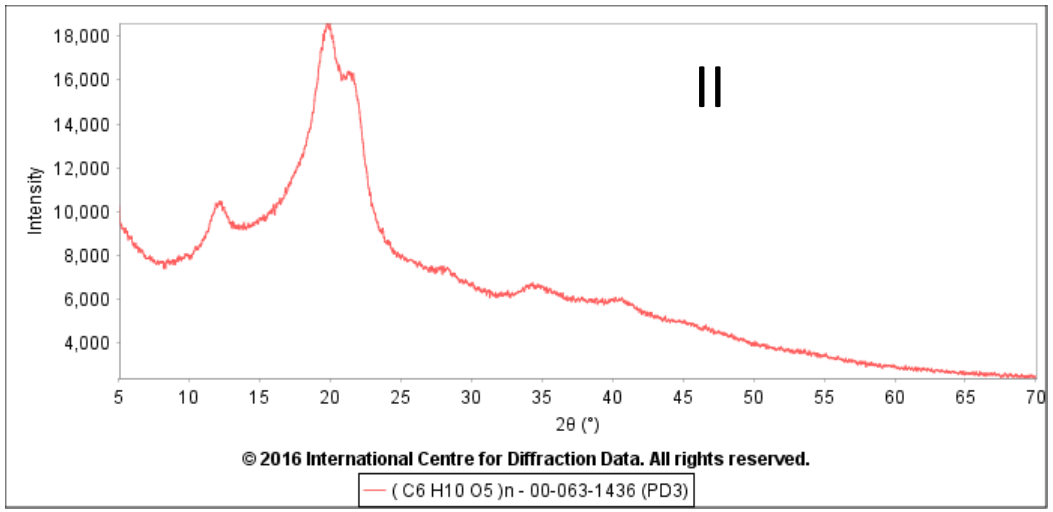


Excipient polymers PDF raw data patterns (PD3)

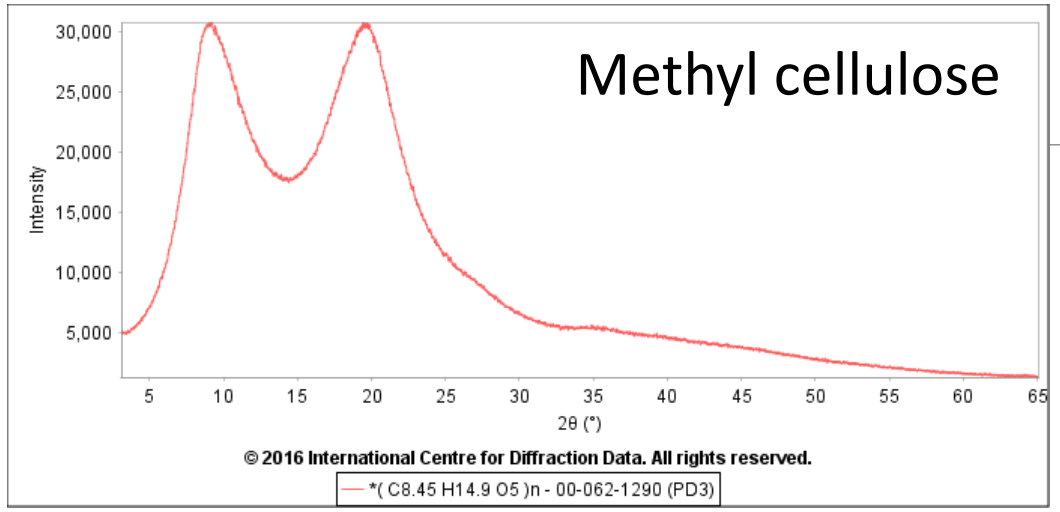
Cellulose

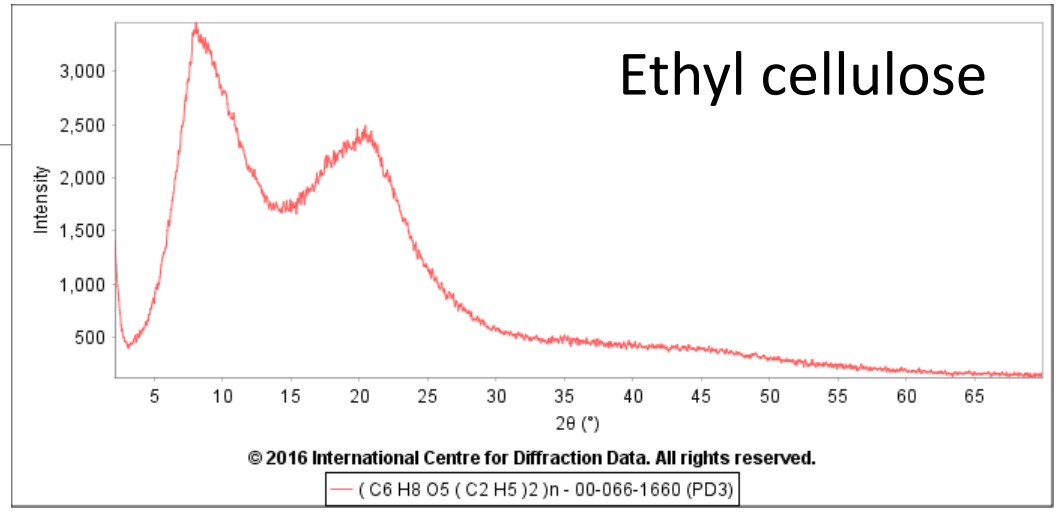


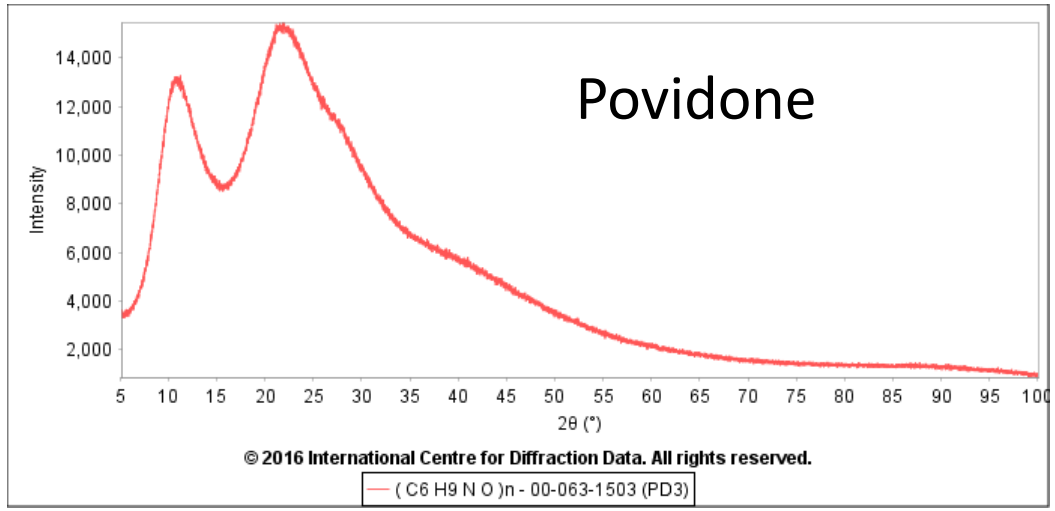


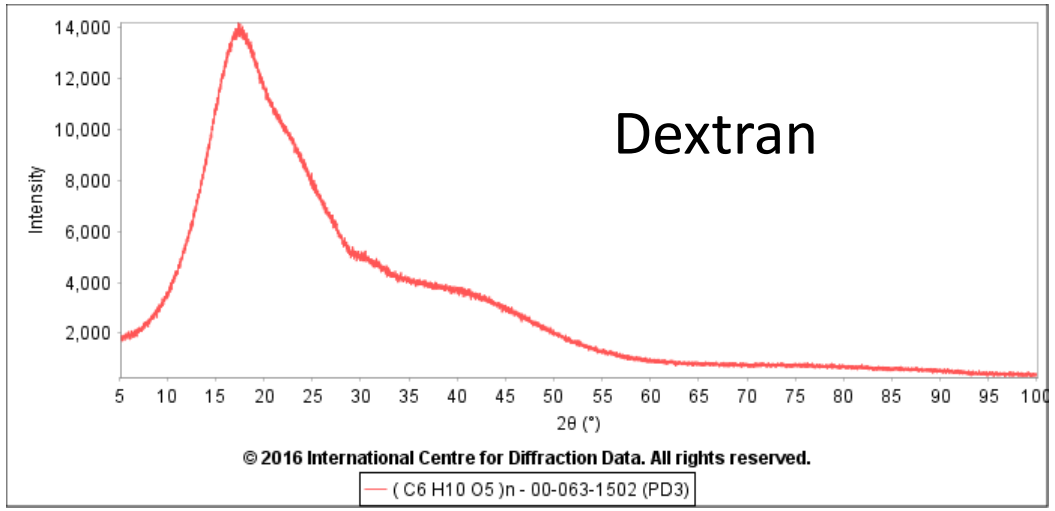


Excipient polymers PDF raw data patterns (PD3)



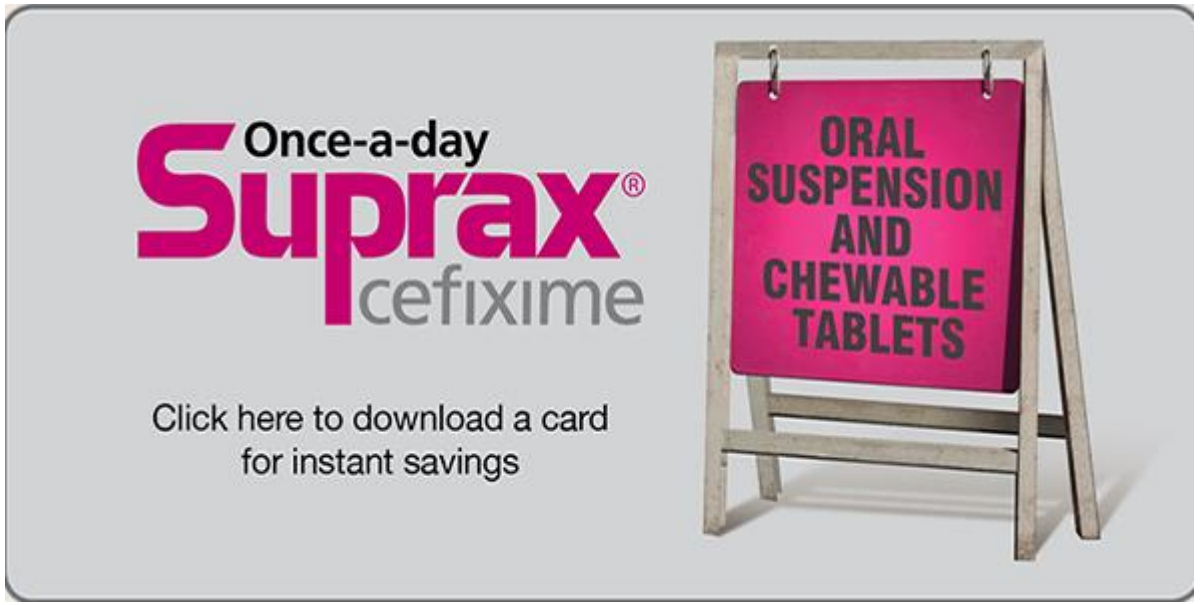




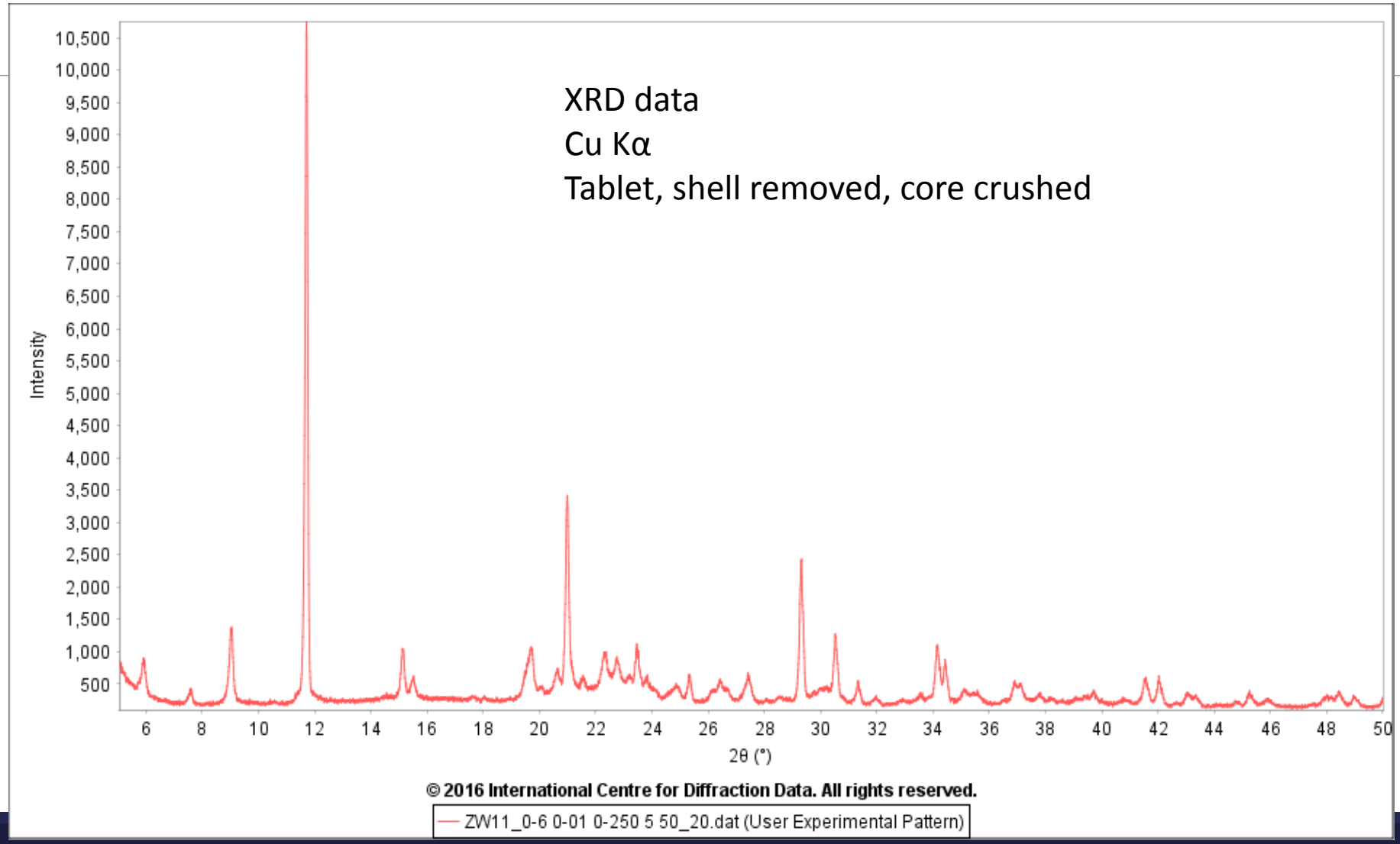


XRD analysis of Suprax®

Suprax (API: Cefixime $3H_2O$) is an antibiotic used for the treatment bacterial infections



Phase identification – Suprax core



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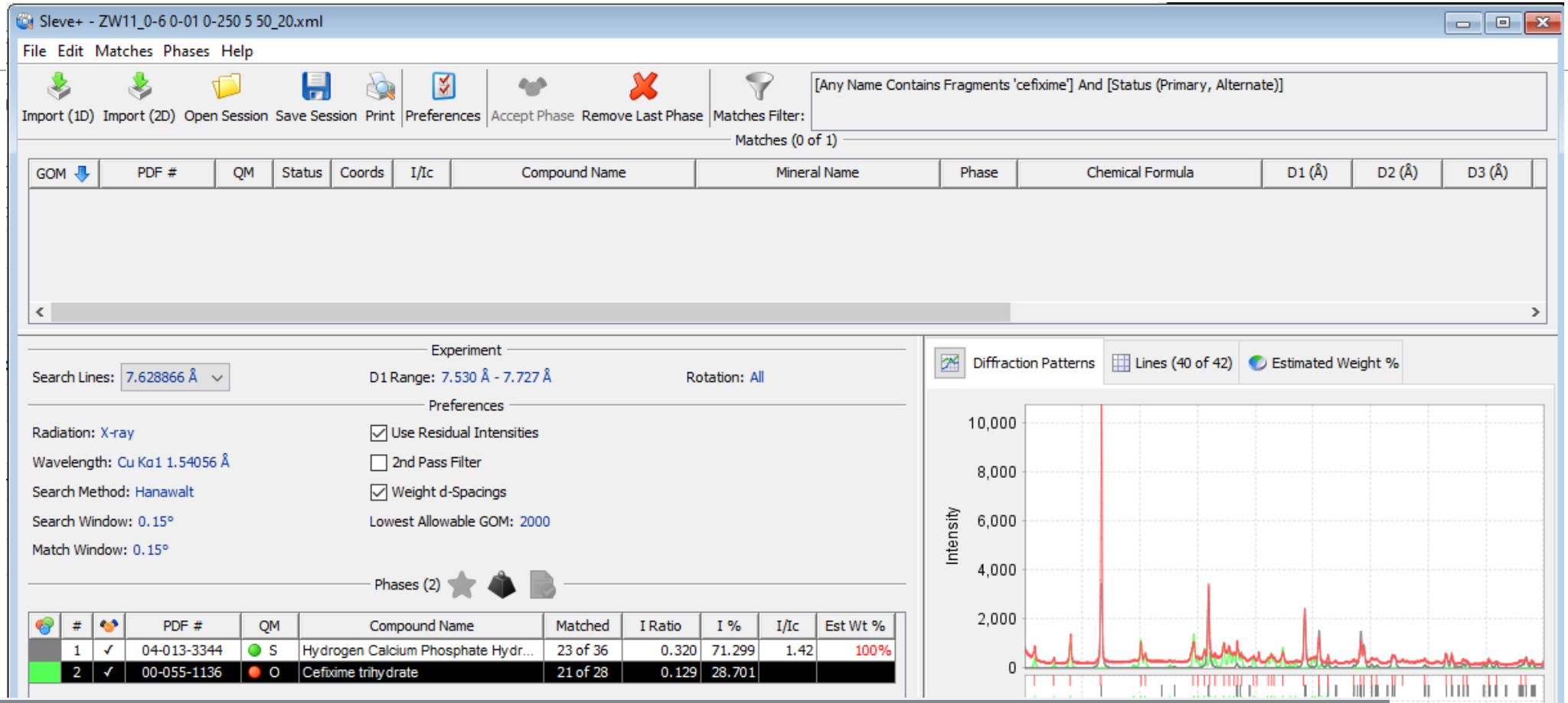
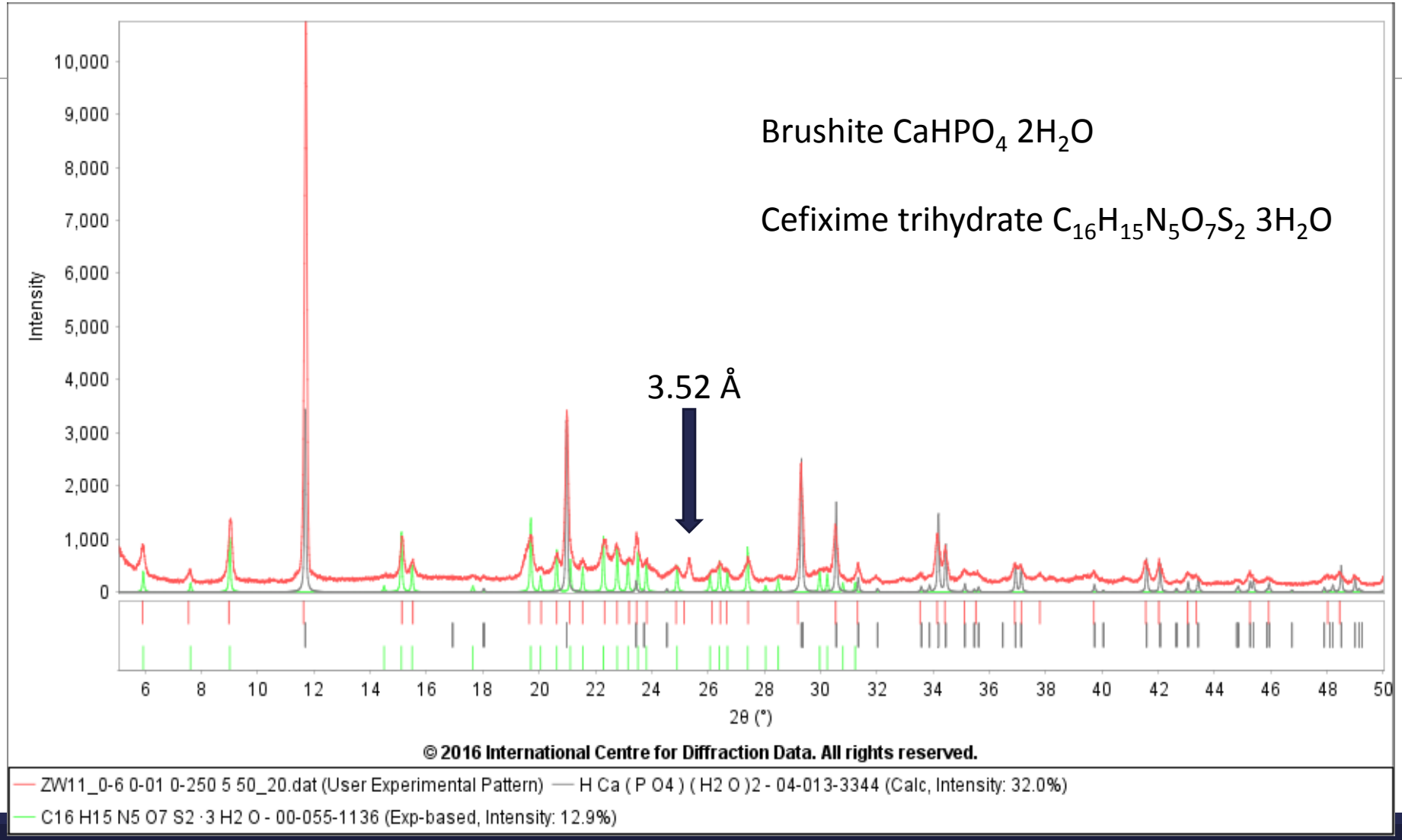
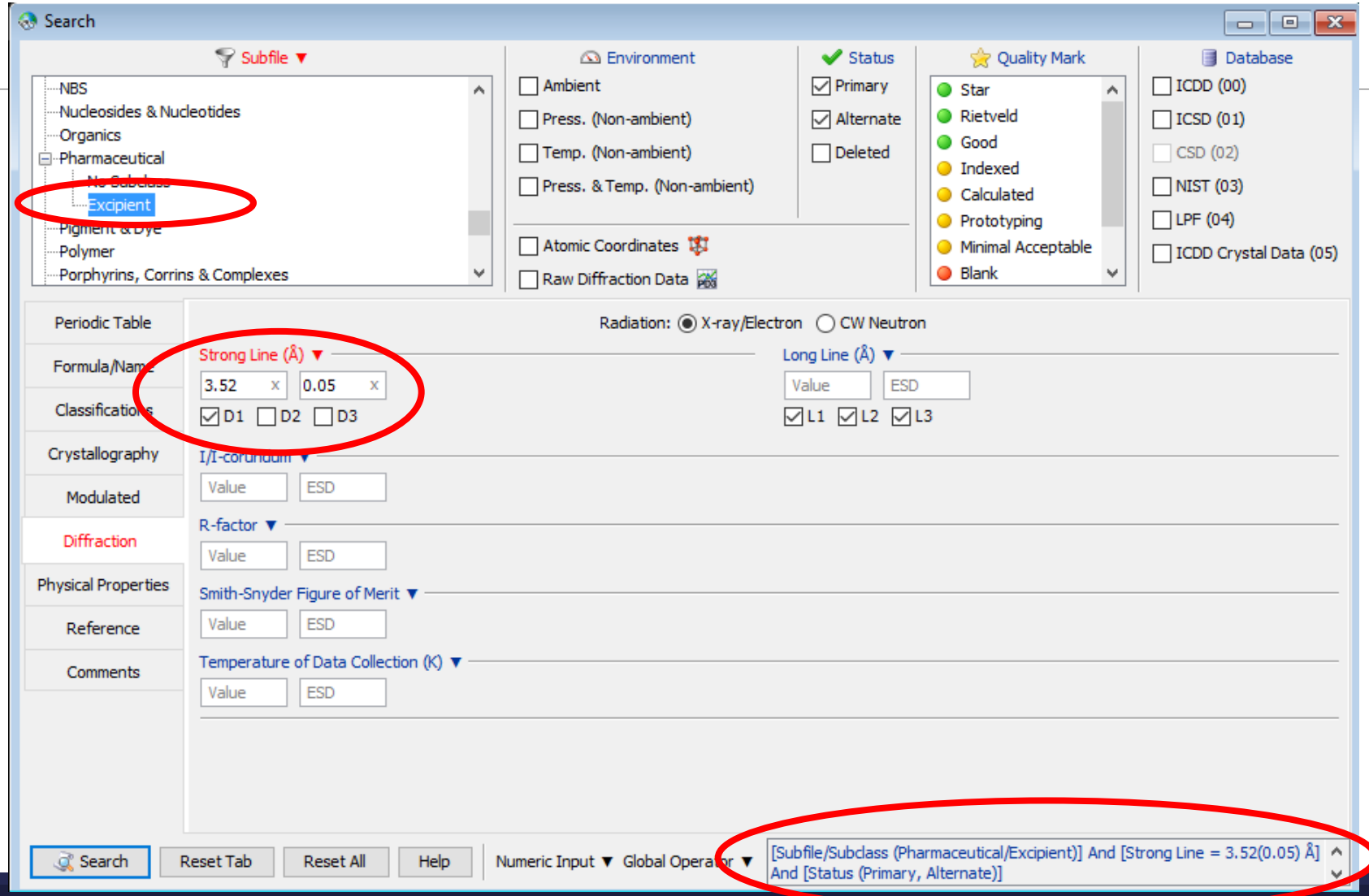


#		PDF #	QM	Compound Name	Matched	I Ratio	I %	I/Ic
1	✓	04-013-3344	S	Hydrogen Calcium Phosphate Hydr...	23 of 36	0.320	71.299	1.42
2	✓	00-055-1136	O	Cefixime trihydrate	21 of 28	0.129	28.701	

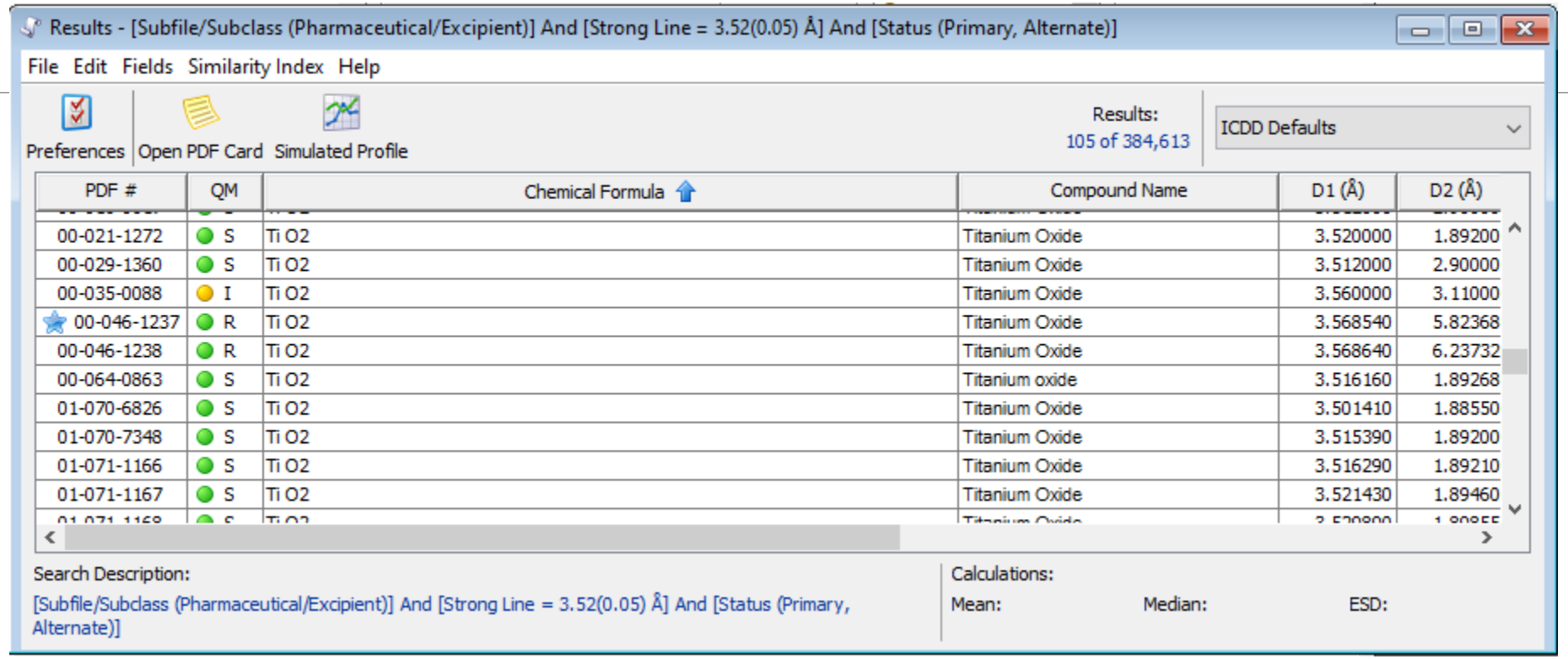
Phase identification – Suprax core



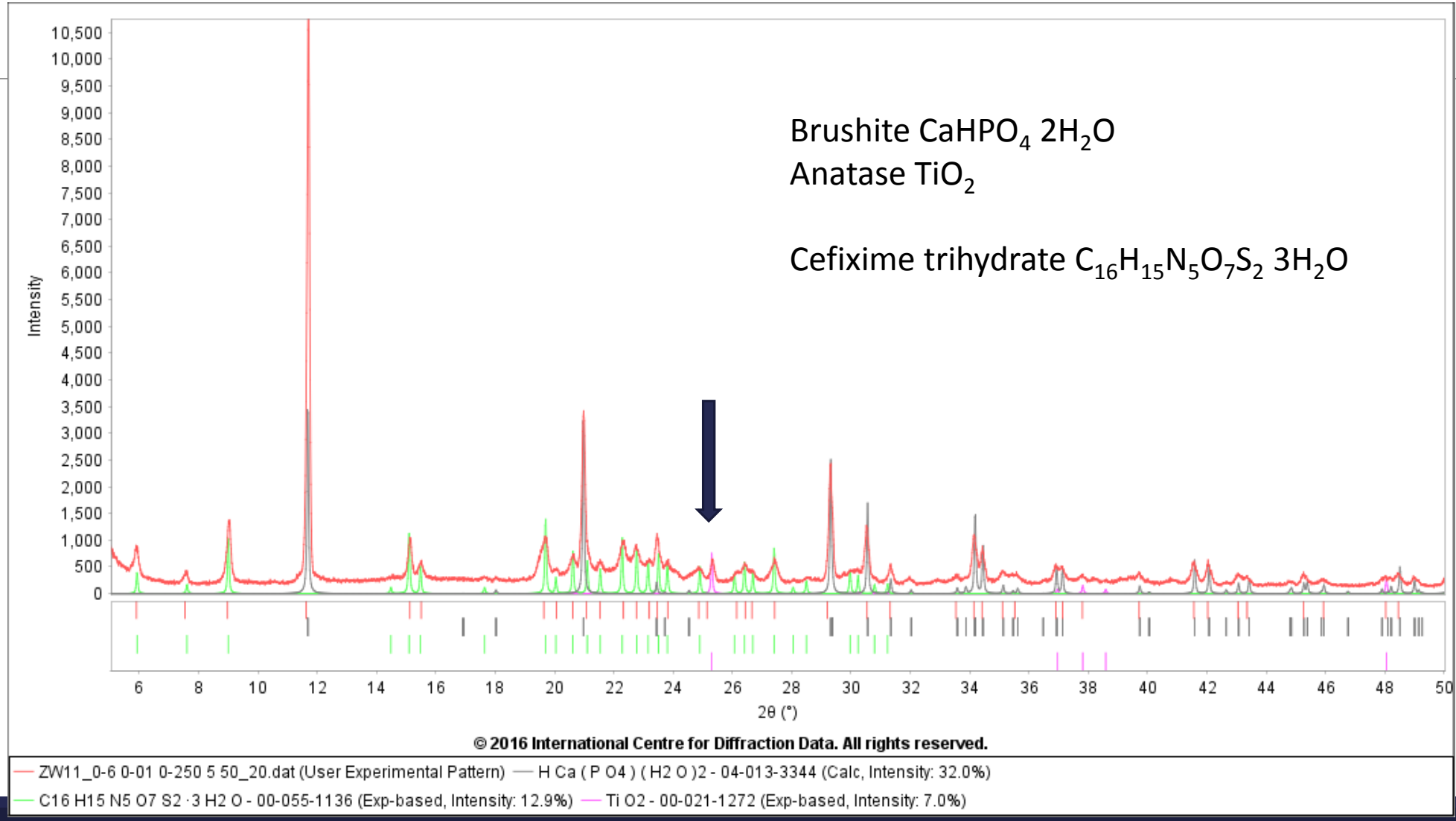
PDF Data Mining



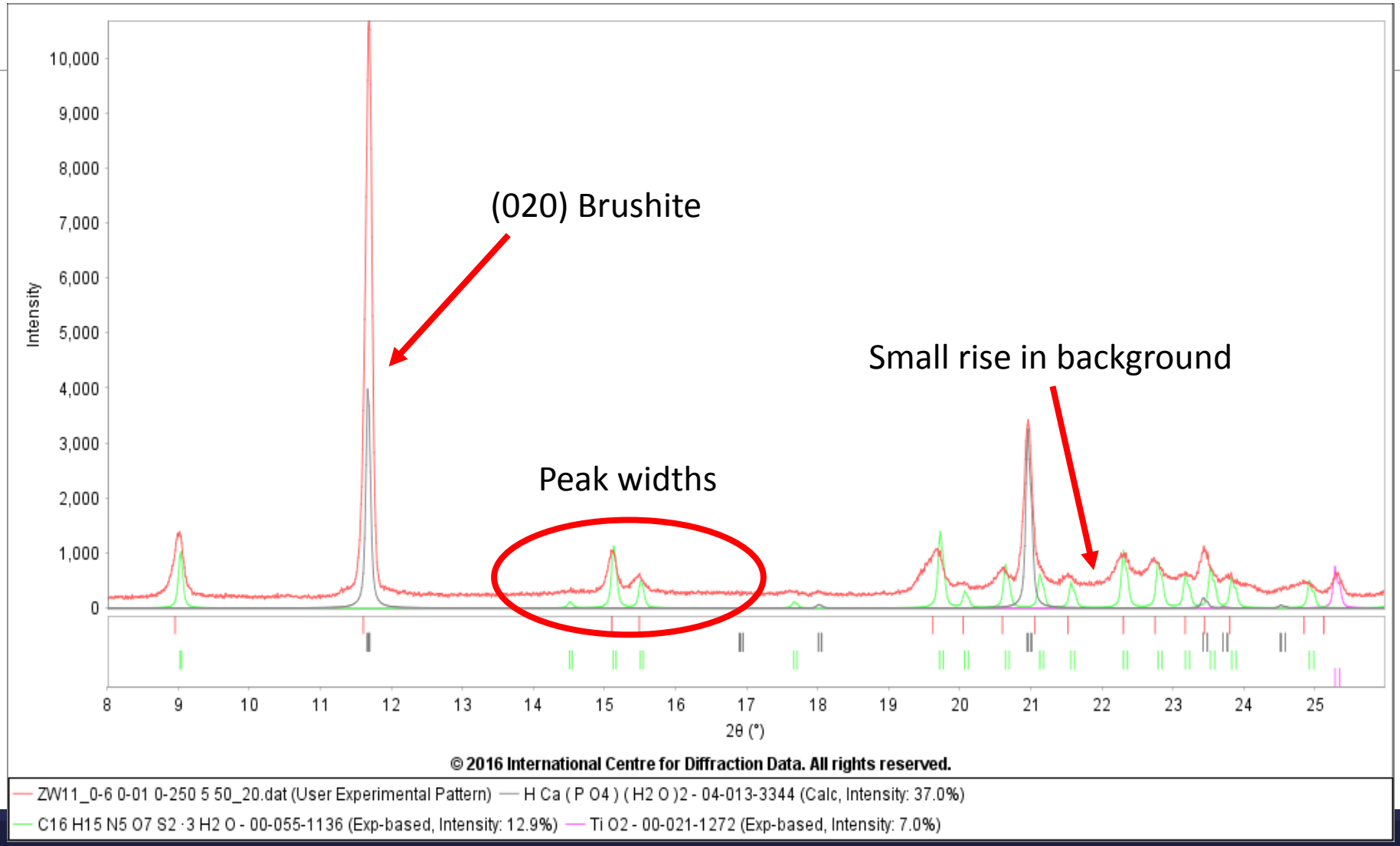
PDF Data Mining



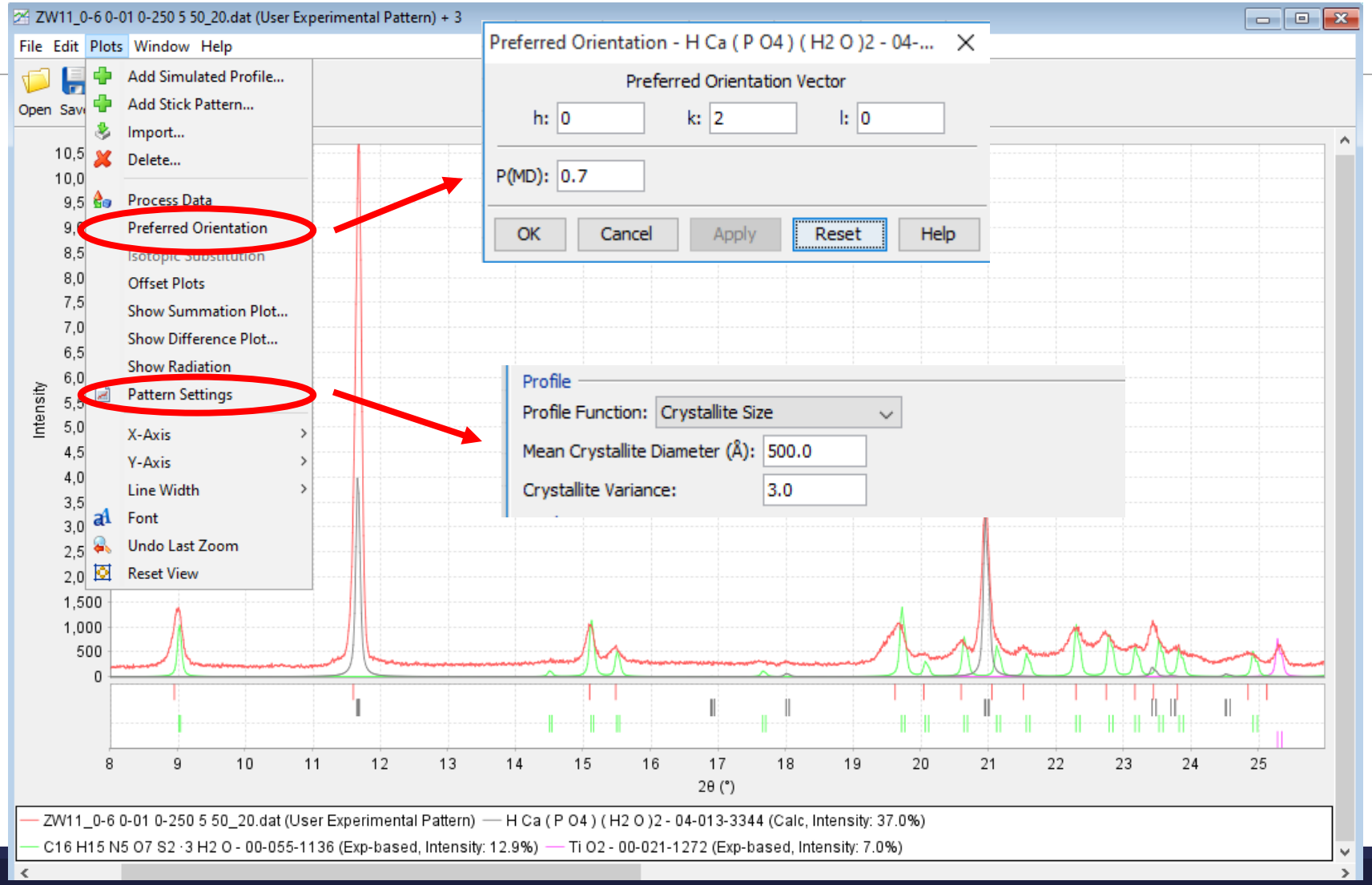
Phase identification – Suprax core



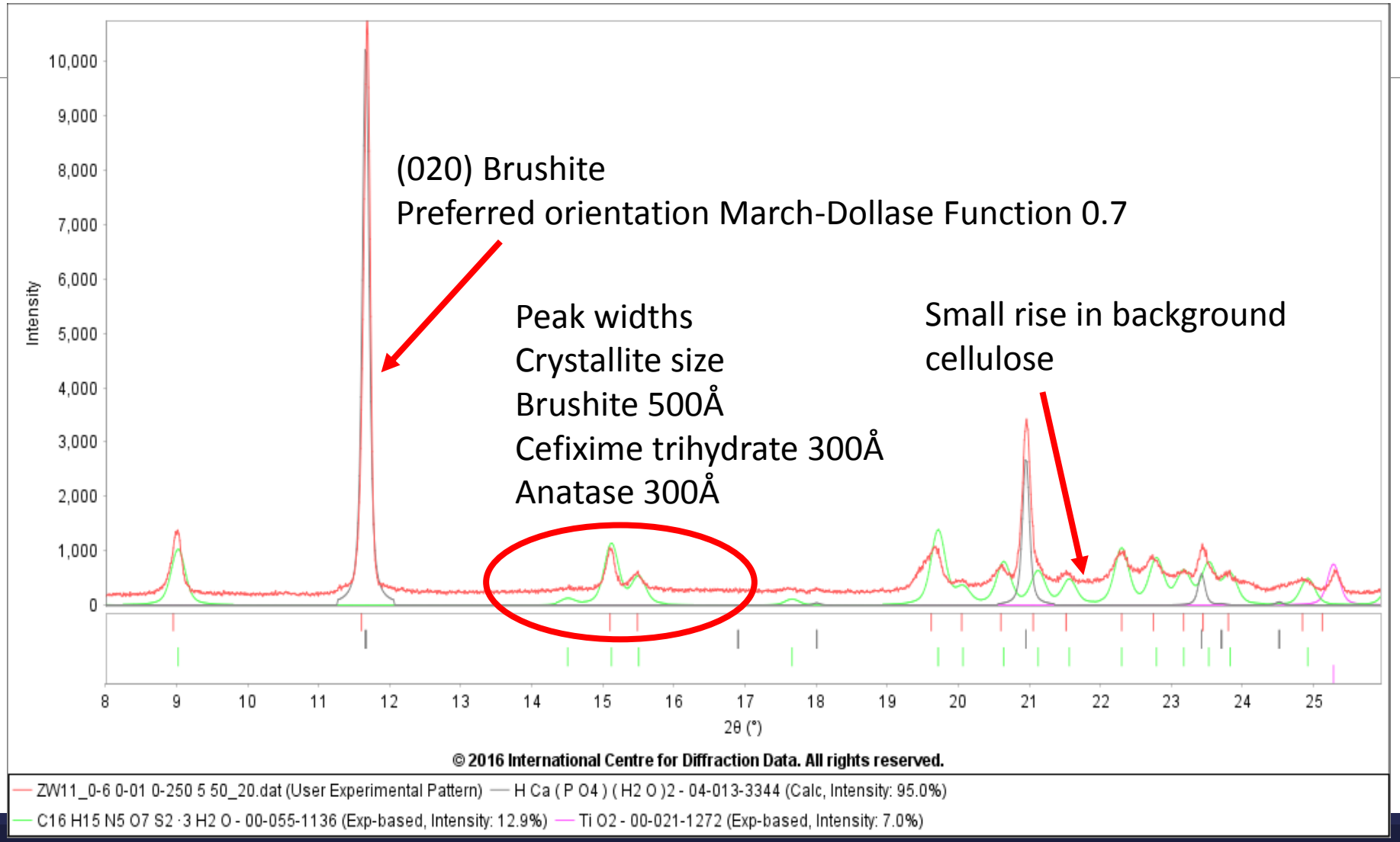
Phase identification – Suprax core



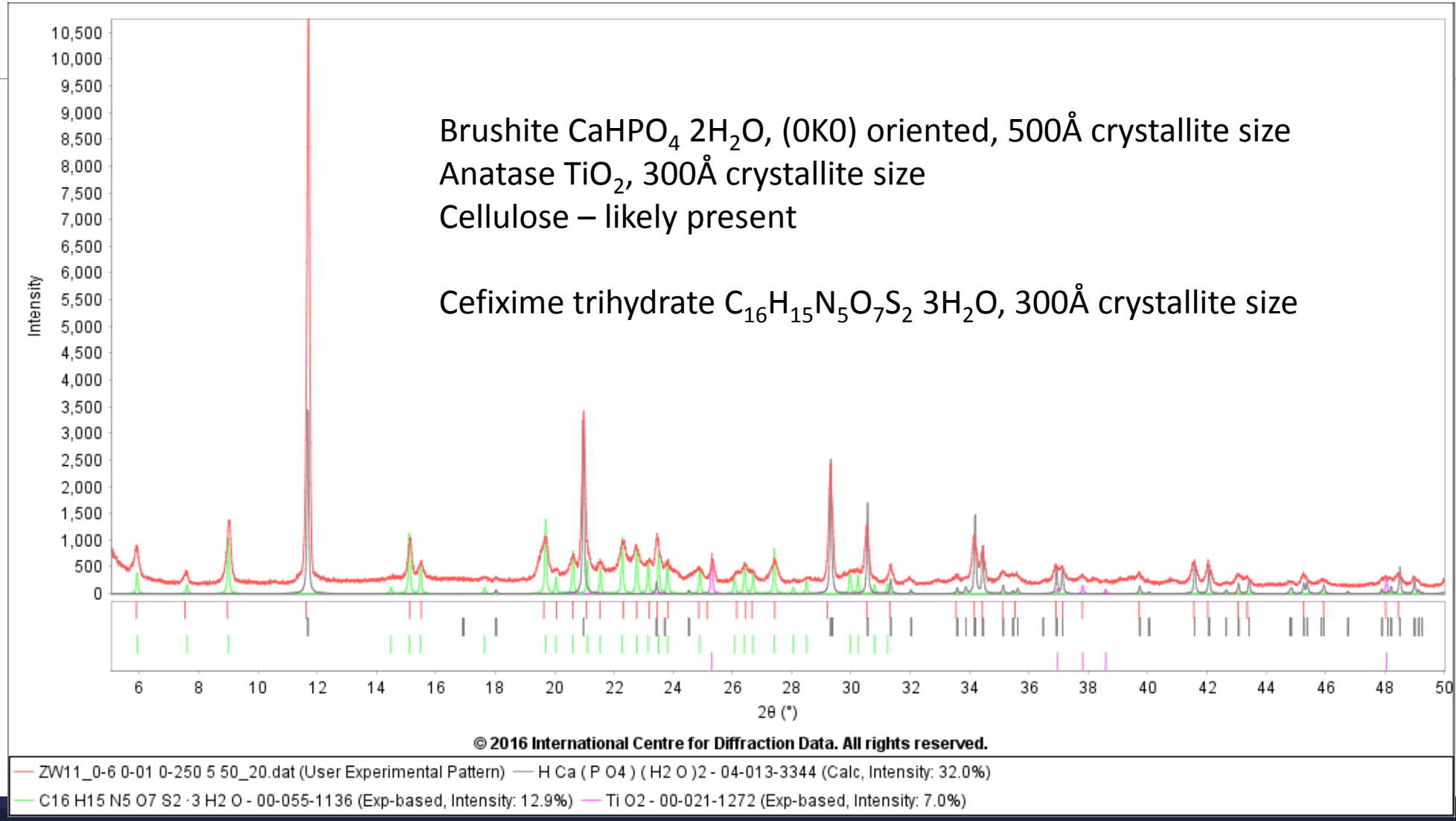
Phase identification – Suprax core



Phase identification – Suprax core



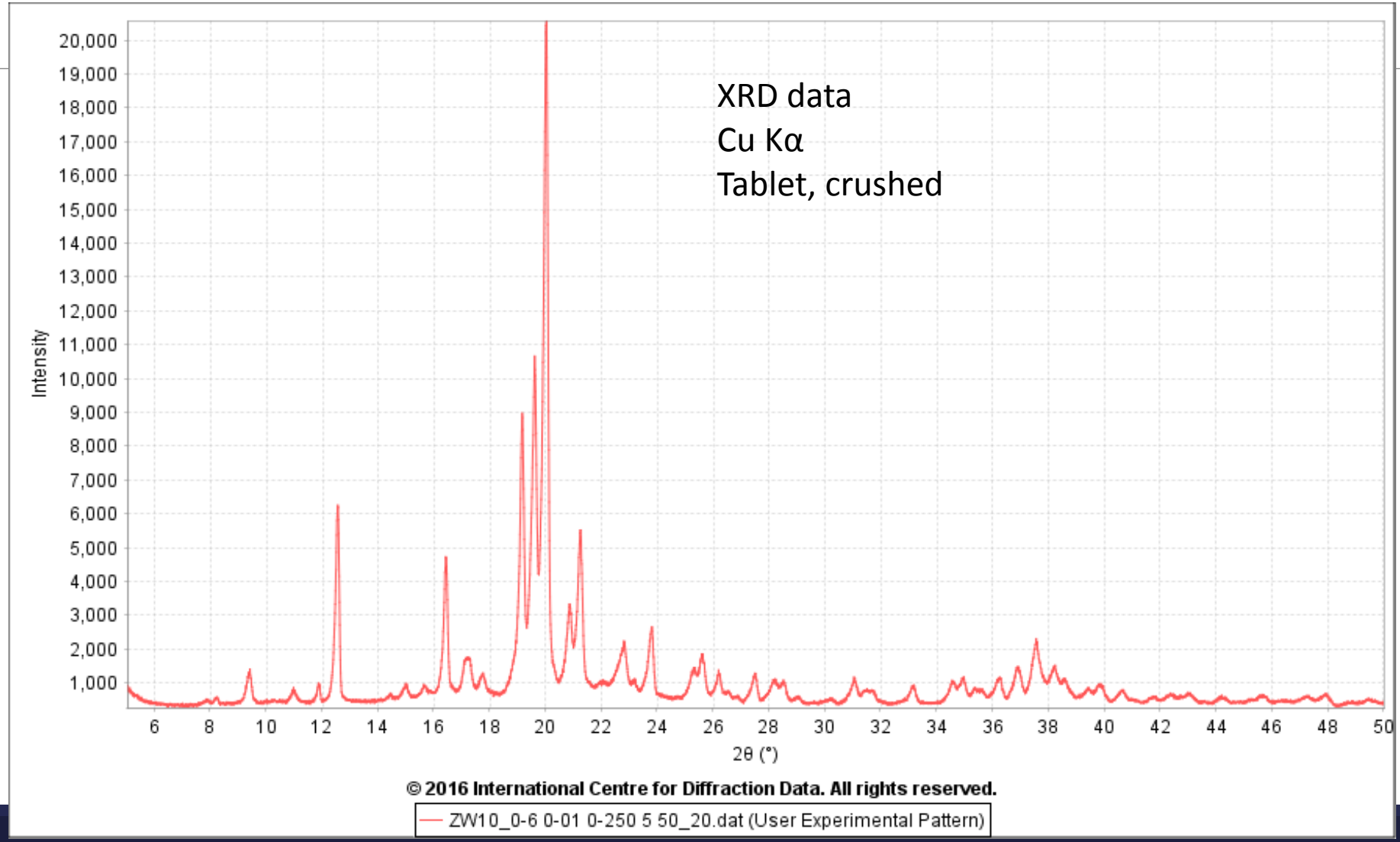
Phase identification – Suprax core



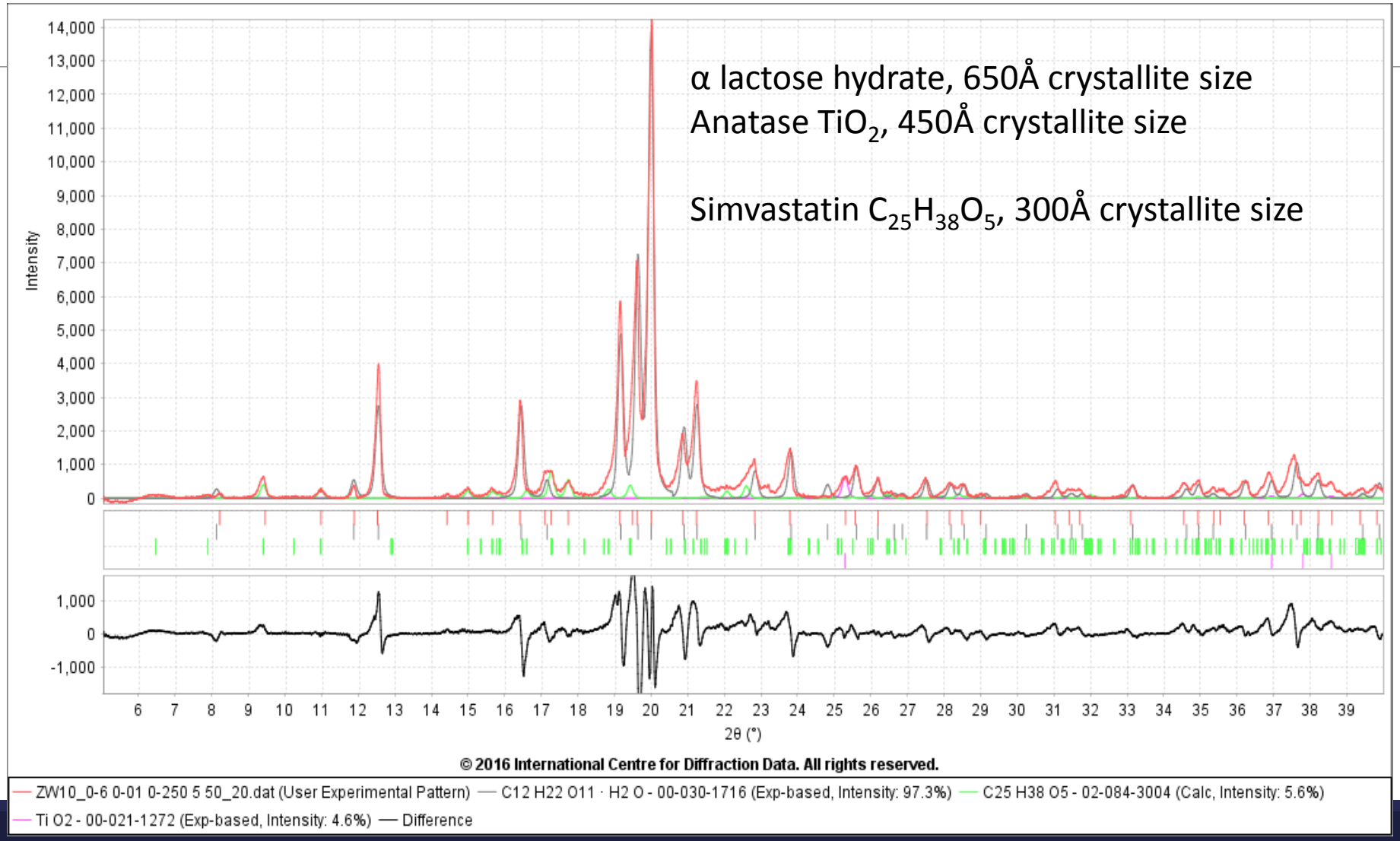
XRD analysis of Zocor® generic

Zocor generic (API: Simvastatin) is a statin used to lower blood cholesterol

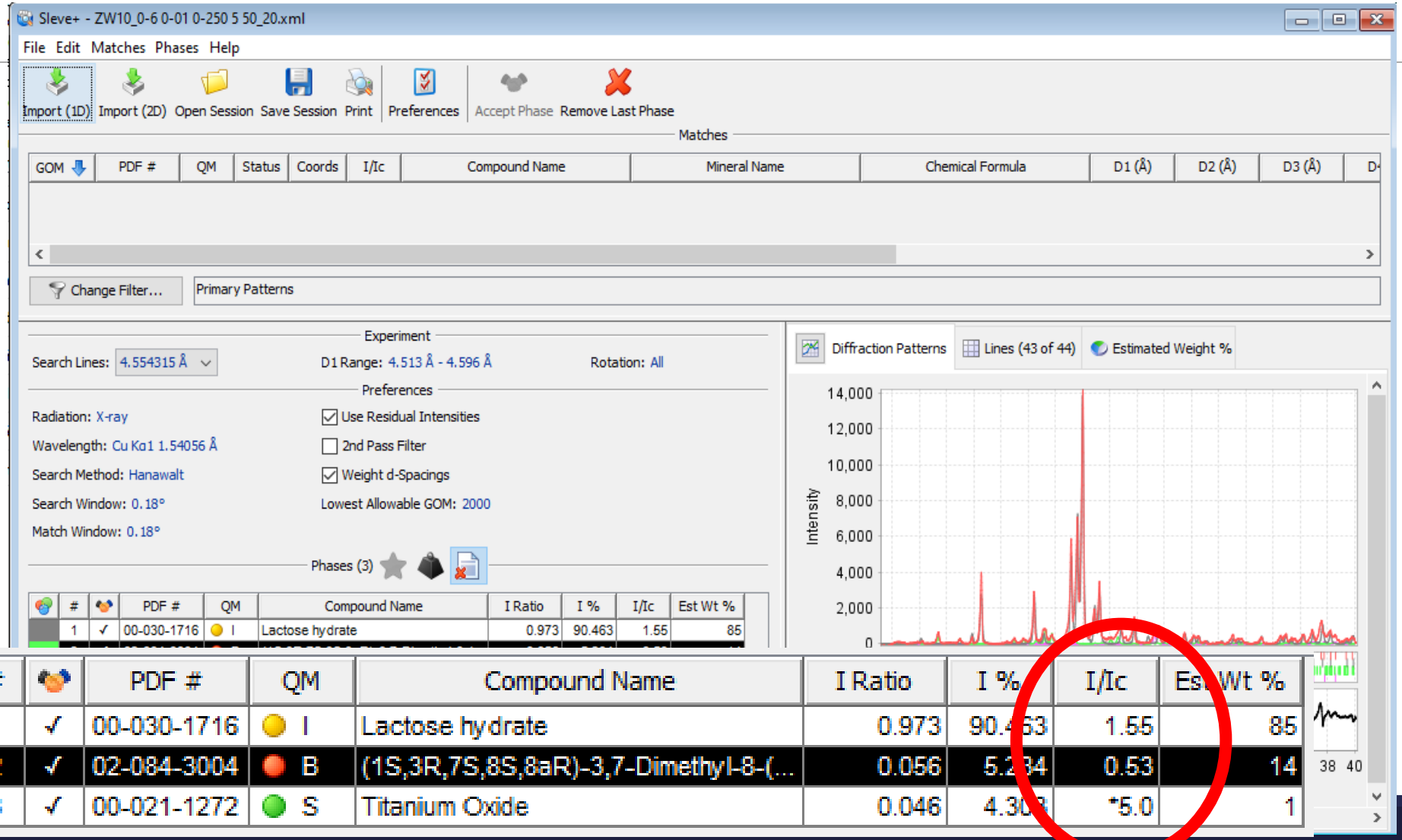
Phase identification – Zocor generic core



Phase identification – Zocor® generic



Phase identification – Zocor® generic



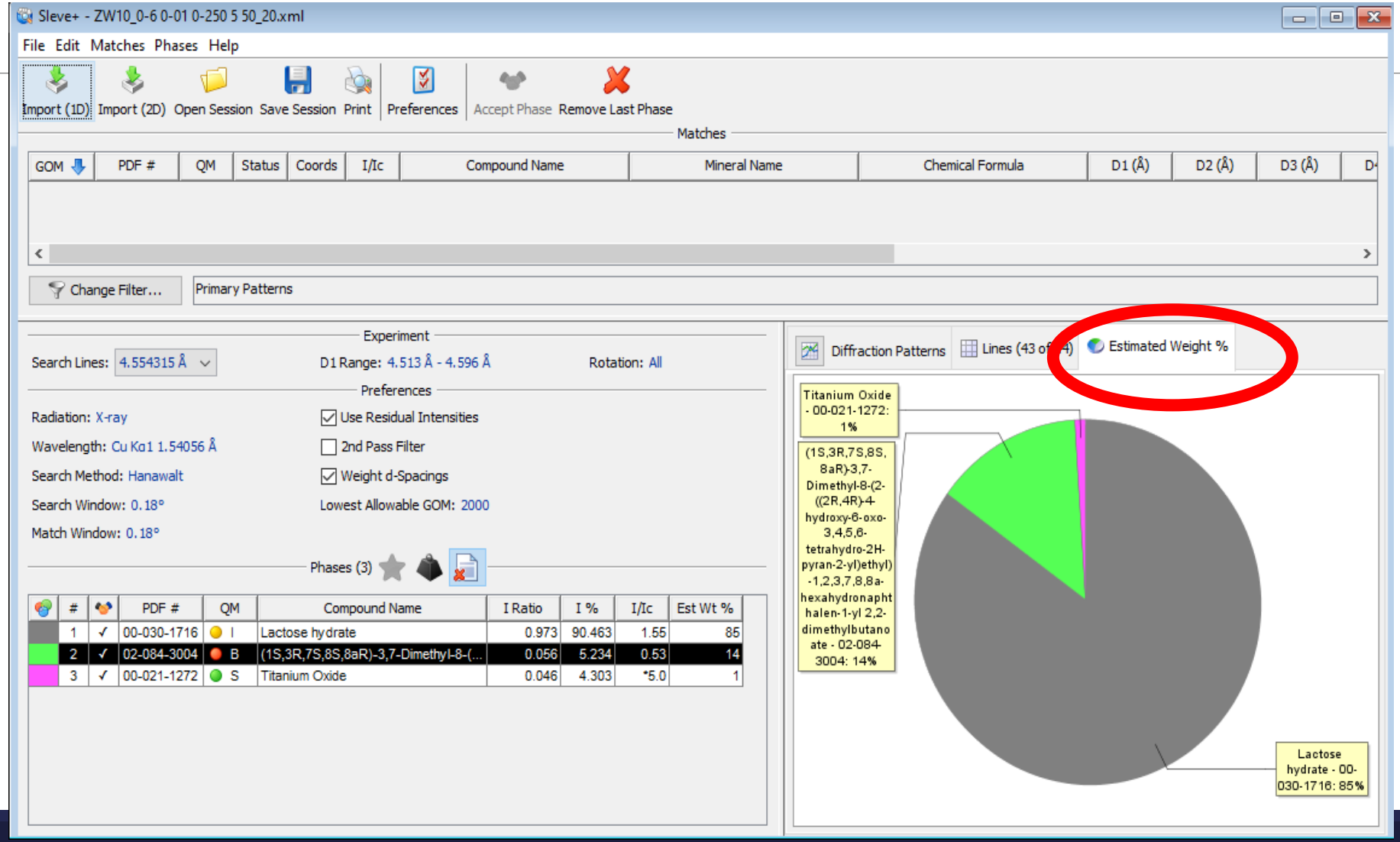
#		PDF #	QM	Compound Name	I Ratio	I %	I/Ic	Est Wt %
1	✓	00-030-1716	I	Lactose hydrate	0.973	90.463	1.55	85
2	✓	02-084-3004	B	(1S,3R,7S,8S,8aR)-3,7-Dimethyl-8-(...	0.056	5.234	0.53	14
3	✓	00-021-1272	S	Titanium Oxide	0.046	4.303	*5.0	1

RIR method for multiphase sample

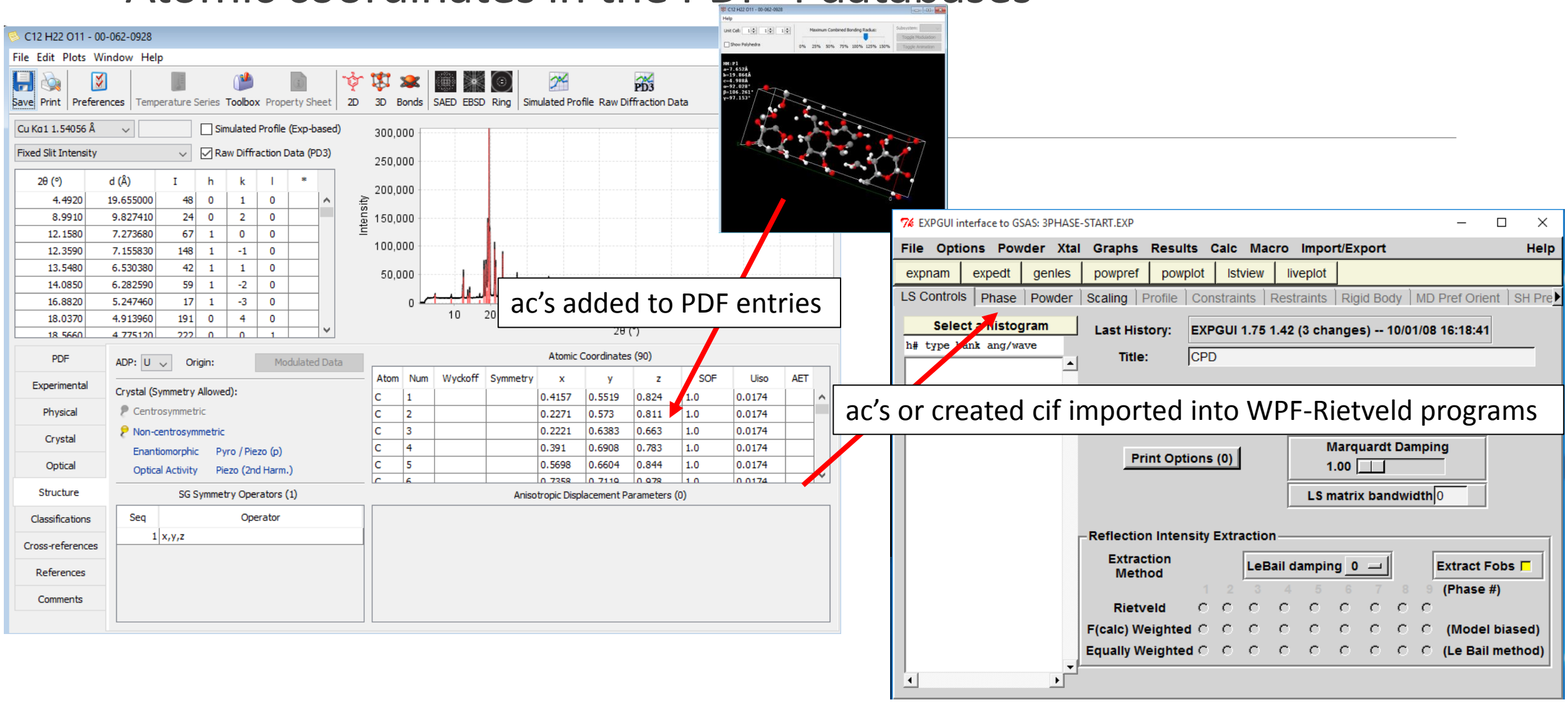
$$\sum_{j=1}^{n} X_j = 1$$

$$X_\alpha = \frac{I_{(hkl)\alpha}}{RIR_\alpha I^{rel}_{(hkl)\alpha}} \left[\frac{1}{\sum_{j=1}^{n} \left(I_{(hkl)'j} \Big/ RIR_j I^{rel}_{(hkl)'j} \right)} \right]$$

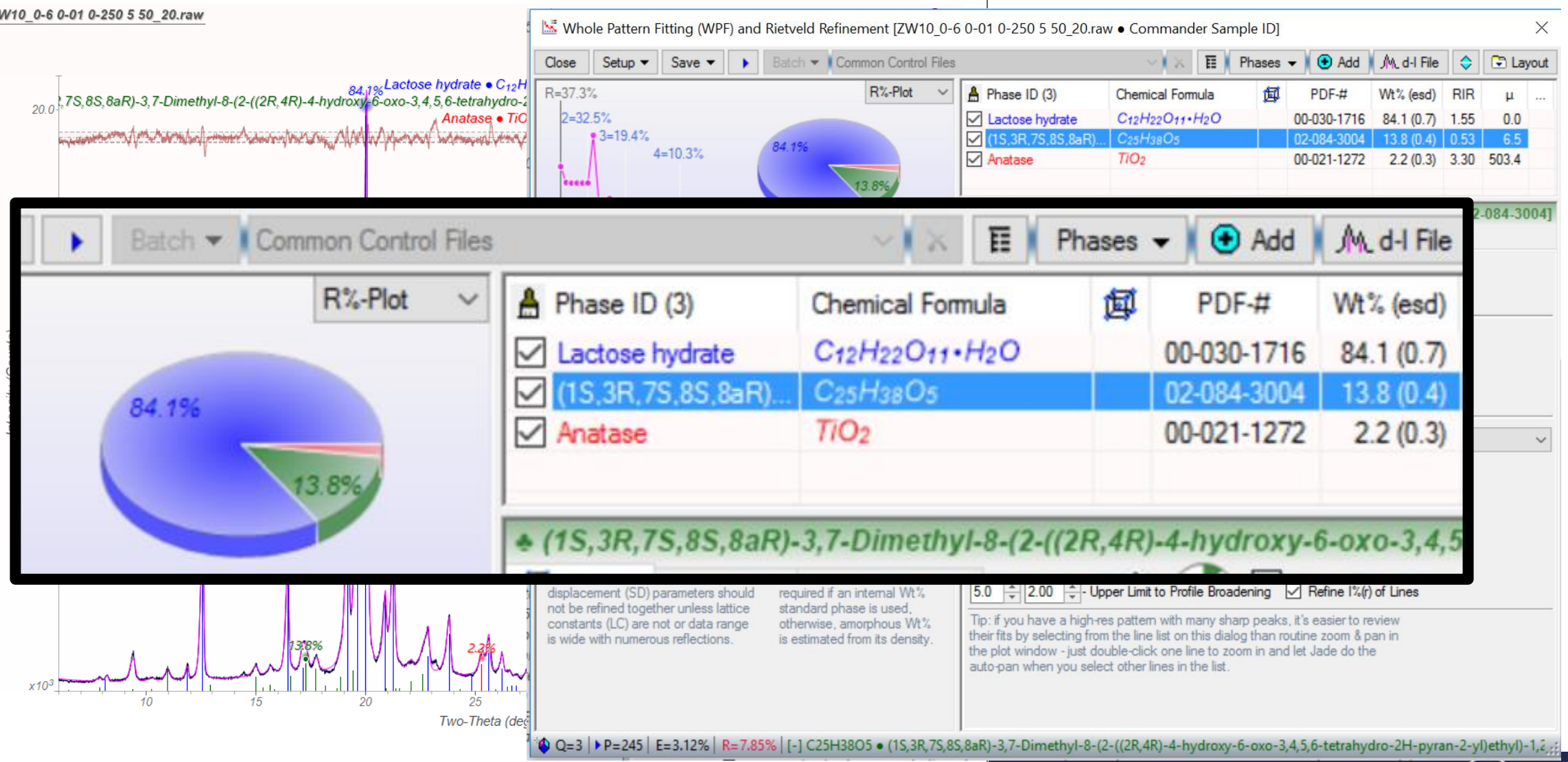
Phase identification – Zocor® generic



Atomic coordinates in the PDF-4 databases



Phase identification – Zocor® generic



Phase identification – Zocor® generic

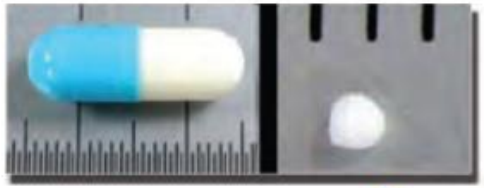
PDF-4 SIEVE+ RIR		WPF RIETVELD	
α lactose hydrate	85 wt.%	α lactose hydrate	84.1(7) wt.%
Simvastatin $C_{25}H_{38}O_5$	14 wt%	Simvastatin $C_{25}H_{38}O_5$	13.8(4) wt%
Anatase TiO_2	1 wt.%	Anatase TiO_2	2.1(3) wt.%

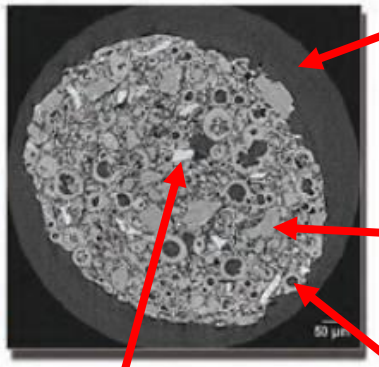
The RIR method works well when samples are randomly oriented and I/Ic values are known

Keys to successful excipient phase analysis

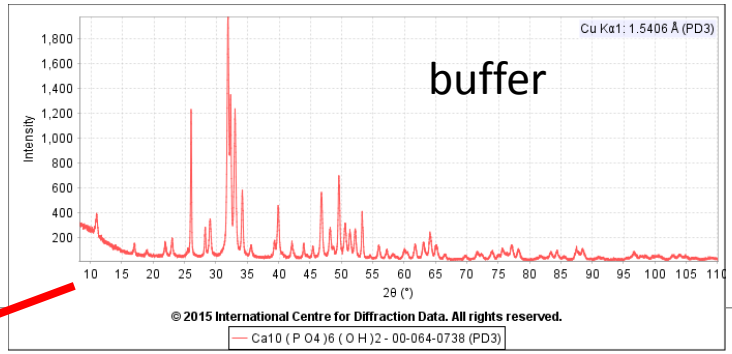
- Research the pharmaceutical – understand the drug and formulary being evaluated
- Sample preparation – particle size, sample thickness, specimen displacement
- Instrument alignment – run calibration standards to confirm proper operation
- Data collection – use the proper count time for good counting statistics
- Reference database – must have pharmaceutical and excipient subfiles, editorially reviewed

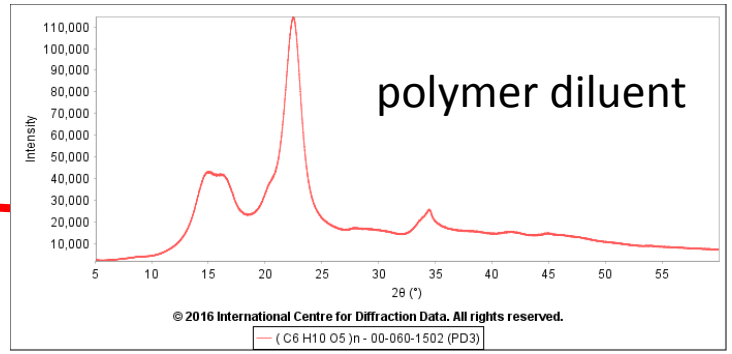
The future

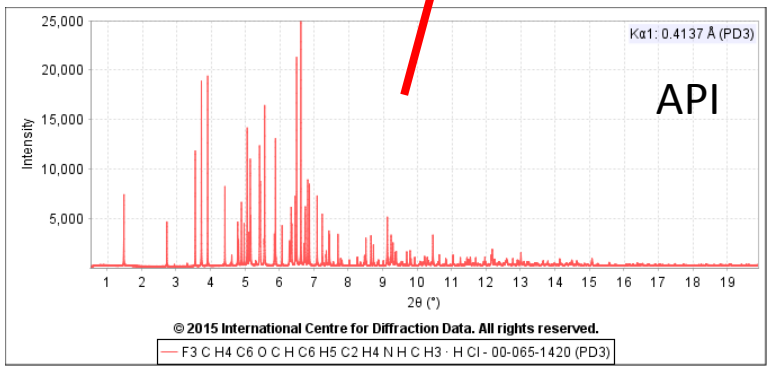


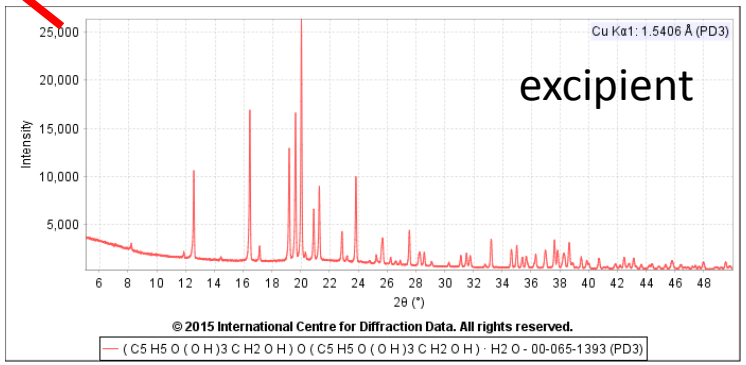


3d X-ray tomography
(courtesy of Rigaku)





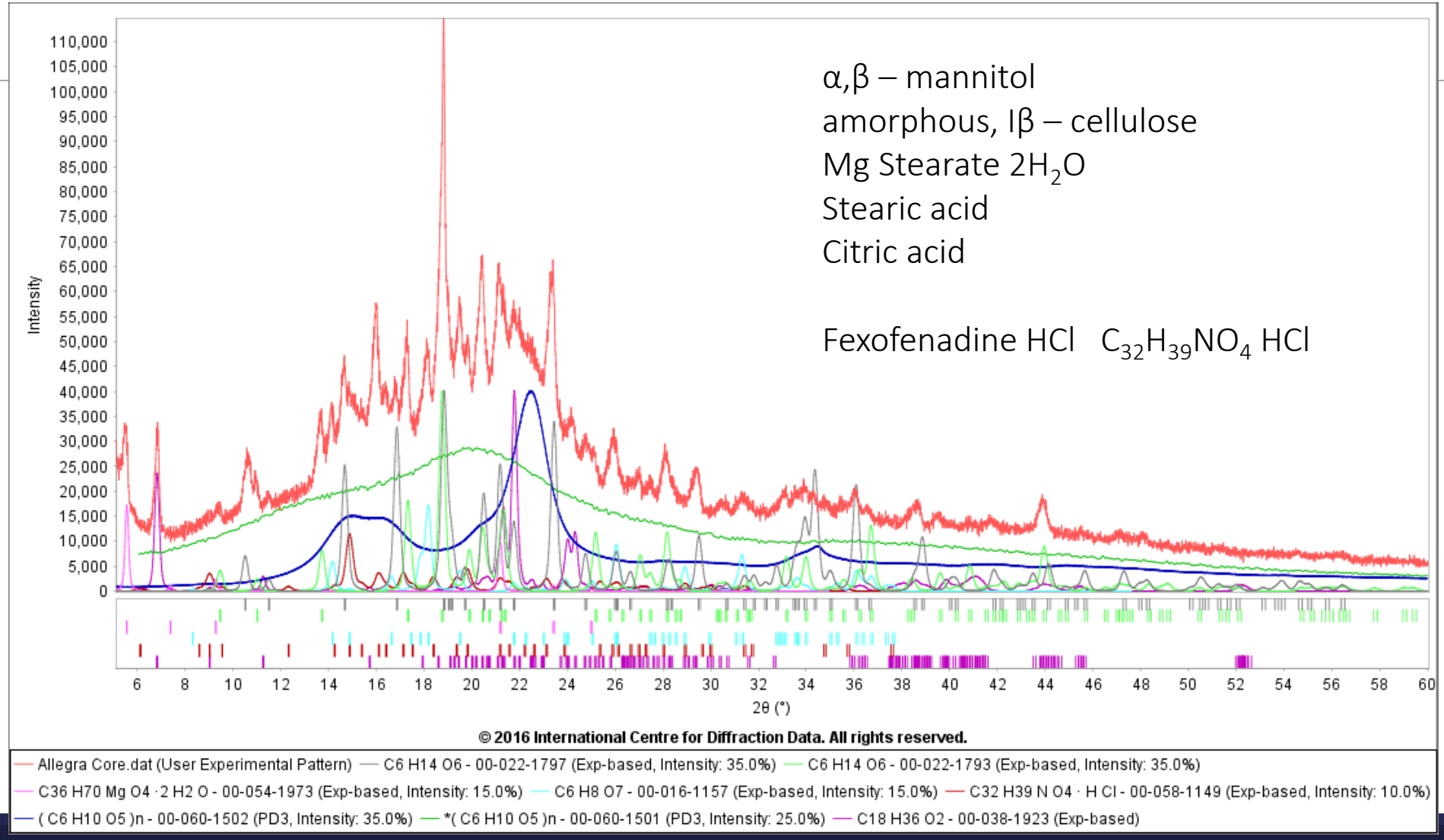




XRD analysis of Allegra®

Allegra (API: Fexofenadine HCl) is an antihistamine used for the treatment of hay fever and related allergy symptoms.

Phase identification – Allegra® core



Phase identification – Allegra® shell