Improving the Pharmaceutical Subfile for the ICDD PDF-4/Organics Database

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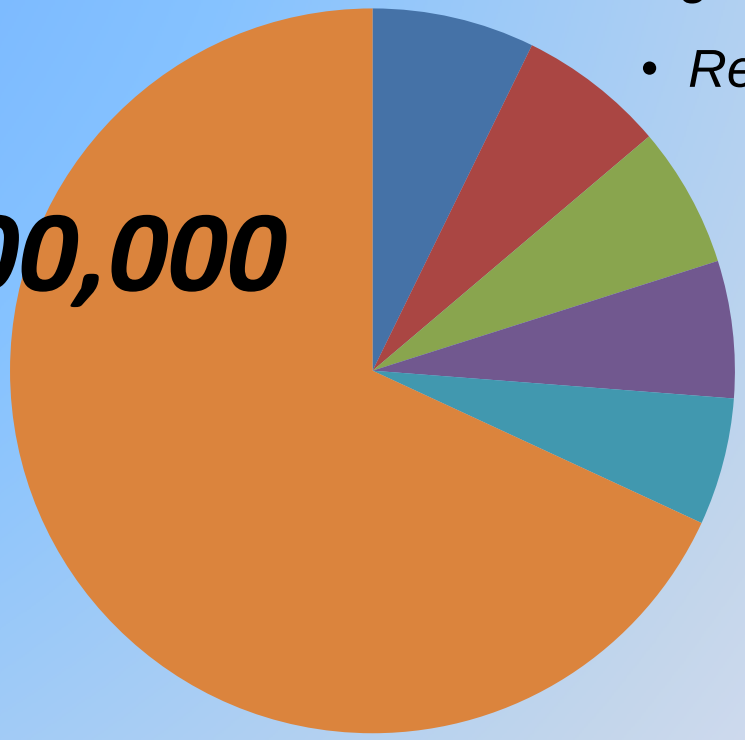
Pharmaceutical Market



$320,000,000,000

- *Oncologics*
- *Respiratory agents*
- *Lipid regulators*
- *Antidiabetics*
- *Antipsycotics*

- Total health care spending reached $320 billion in 2011 and five therapy areas account for one third of it[1]:

[1]http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011

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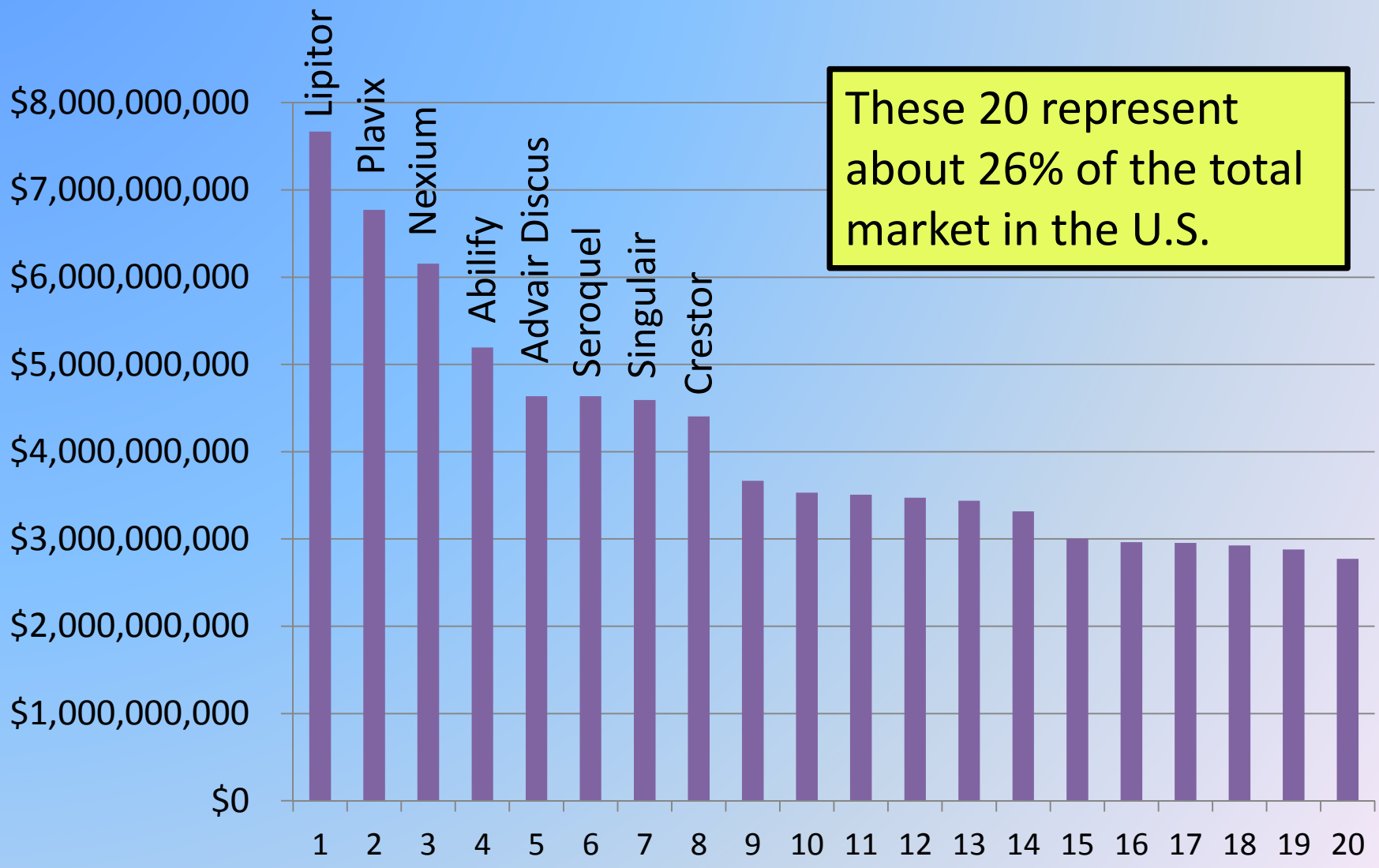
Top 20 Brand Name Drugs - U.S. Sales 2011



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Top-200 Pharmaceutical XRPD Patterns

- Of the 200 top brand name drugs by 2011 US sales, 54 contain biological macromolecules and polymer active pharmaceutical ingredients (APIs).
- The remaining 146 contain small molecule APIs.
- The objective of this project is to assess the coverage of these 146 APIs in the PDF-4+/Organics database and obtain high-quality X-ray powder diffraction (XRPD) patterns for missing materials or those with low-quality patterns. Additionally ascertain crystal structures with atomic coordinates where possible.

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One API, How Many Crystal Forms?

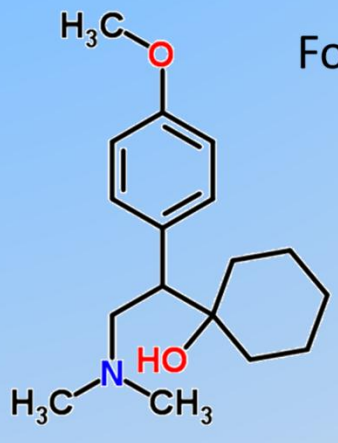
For each small molecule API, there can be many related patterns in the PDF:

- Salts
- Solvates
- Co-crystals
- Free base (or acid)
- Hydrates
- Enatiomorphs (chirally pure or racemic)

API

Venlafaxine HCl

Forms I, II, VI



- Venlafaxine (enantiomorphs) Forms I, III
- Venlafaxine (racemic) Forms I, II
- Venlafaxine HCl hydrate
- Venlafaxine saccharinate
- Venlafaxine HBr

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PDF-4+/Organics 2013

- Unique APIs in the 146 brand name small molecule drugs = 147.
- API and API-related patterns in PDF = 618*
- API patterns = 252 (covers 83 of the 147 unique APIs)
- API patterns with atomic coordinates = 36** (This has increased for PDF-4+/Organics 2014)

* Excludes inorganic coordination compounds

** 31 at room temperature

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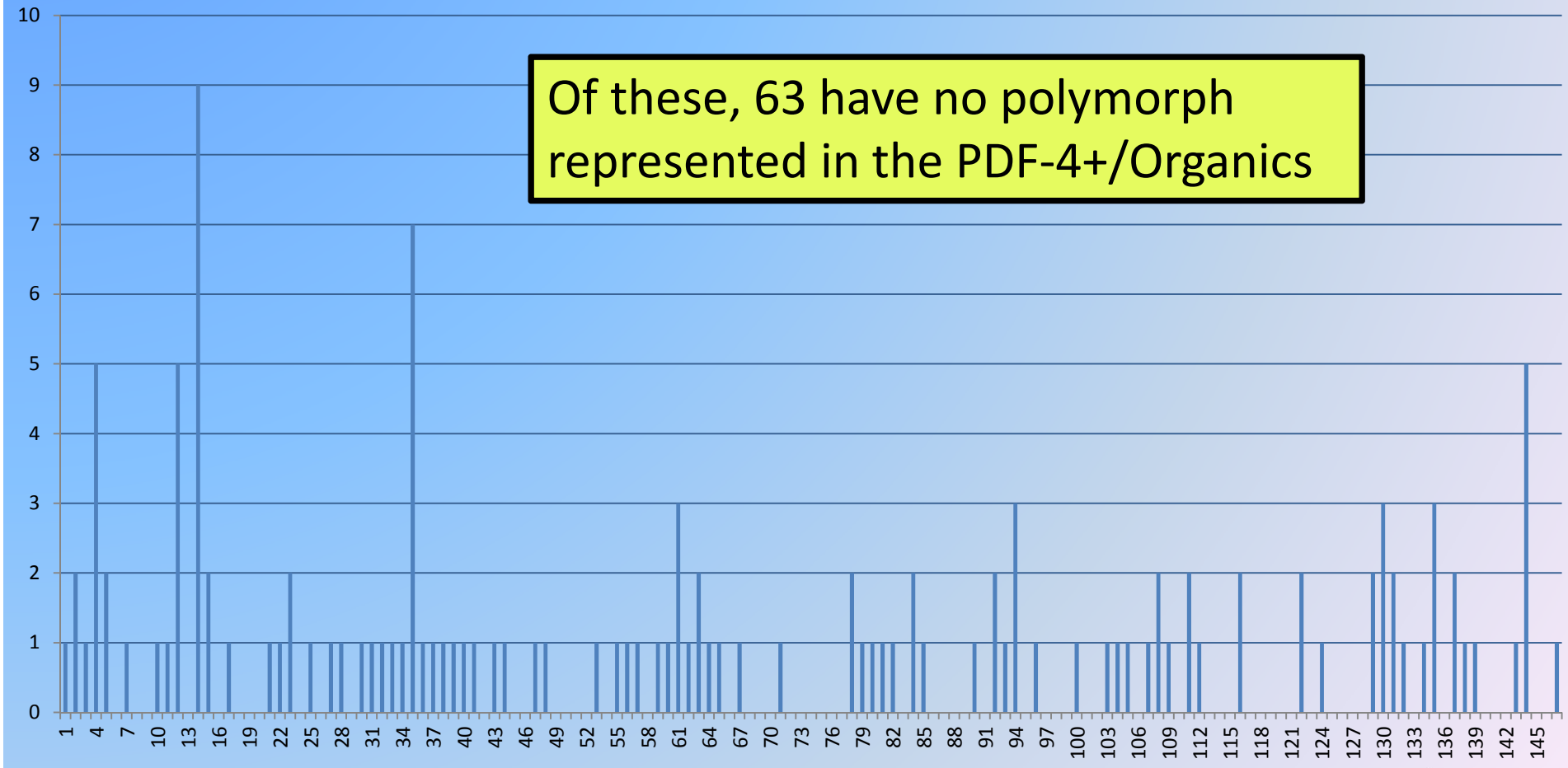
PDF-4+/Organics 2013

Exact API polymorphic representation (exact formula) of the 146 small molecule APIs in the Top-200 pharmaceuticals



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Why Improving the Pharmaceutical Subfile is Important

- High quality room temperature patterns will enable PDF users (such as law enforcement agencies, customs, international security agencies) to identify the APIs above in powder samples.
- Atomic coordinates will allow pharmaceutical companies to do quantitative phase analysis of formulations by the Rietveld method.

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Methodology

1) Collect synchrotron powder diffraction data (11-BM beamline APS) of the 63 APIs without any current patterns
2) Solve crystal structures from the powder data where possible. Synchrotron powder diffraction data facilitates crystal structure solution from powders.
3) Carry out DFT calculations on each structure to determine more accurate H positions and understand the bonding.
4) Publish the new structures in Powder Diffraction.
5) Replace ‘O’ and ‘B’ patterns (41%) with data of higher quality and crystal structures where possible.

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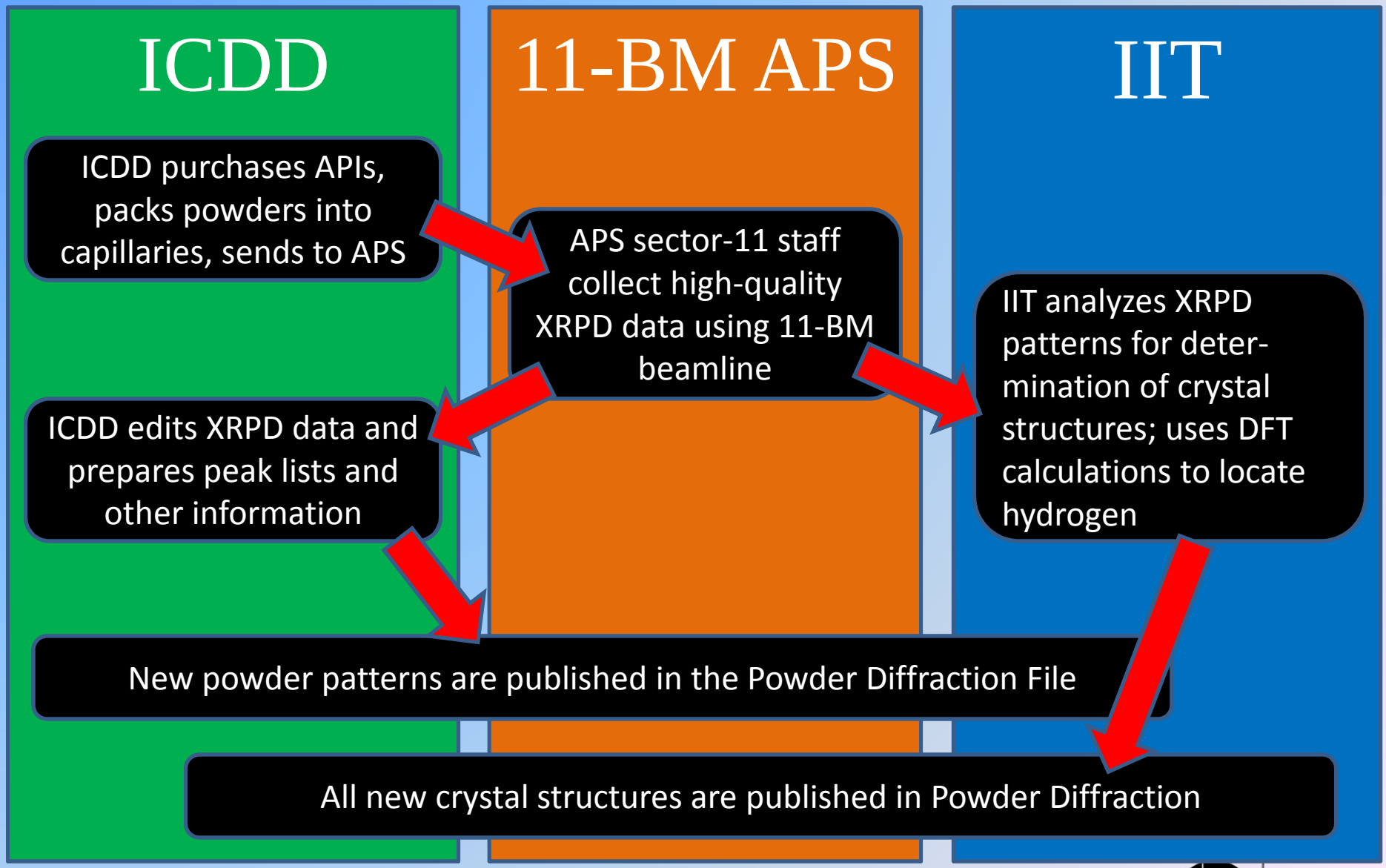
Methodology



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Status of Project

- 34 of these 63 APIs have been obtained from USP, Sigma Aldrich, and other vendors at this time.
- X-ray powder diffraction data have been collected at the APS beamline 11-BM for 16 of these materials via two rapid-access mail-in proposals.
- Materials were packed into Kapton capillaries and data was collected at a wavelength of 0.4139 Å over a range of 0.5° to 50° 2θ (d = 47.42 - 0.4897 Å) .

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First 17

Chemical Name	Formula	Trade Name Examples	
albuterol sulfate	Asthma treatment	Ventolin, Asthalin…	*
capecitabine	Chemotheraputic agent for metastatic cancers	Xeloda	*
risedronate sodium hemipentahydrate	Osteoporosis treatment	Actonel	*
levalbuterol hydrochloride	Asthma treatment	Xopenex	*
tenofovir disoproxil fumarate	Antiretroviral HIV treatment	Viread	
ibandronate sodium	Osteoporosis treatment	Boniva	
Metaprolol succinate	Hypertension	Lopressor	
ziprasidone HCl monohydrate	Schizophrenia / bipolar disorder treatment	Geodon, Zeldox	
paliperidone palmitate (racemic)	Schizophrenia / bipolar disorder treatment	Invega Sustenna	
sitagliptin phosphate monohydrate	Antidiabetic treatment for Type 2 diabetes	Januvia	
valganciclovir hydrochloride	Cytomegalovirus treatment	Valcyte, . . .	
bendamustine hydrochloride	Lymphocytic lukemia treatment	Treanda	
fingolimod hydrochloride	Multiple sclerosis treatment	Gilenya	
raltegravir potassium	HIV infection treatment	Isentress	
piperacillin sodium	Extended spectrum antibiotic	Zosyn (1 of 2 APIs)	
vancomycin hydrochloride	Treatment of gram-positive bacterial infections	Vancocin	

* Crystal Structure determined

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First 16

Chemical Name	Formula	Trade Name Examples	
albuterol sulfate	Asthma treatment	Ventolin, Asthalin…	*
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ibandronate sodium	Osteoporosis treatment	Boniva	
Metaprolol succinate	Hypertension	Lopressor	
ziprasidone HCl monohydrate	Schizophrenia / bipolar disorder treatment	Geodon, Zeldox	
paliperidone palmitate (racemic)	Schizophrenia / bipolar disorder treatment	Invega Sustenna	
sitagliptin phosphate monohydrate	Antidiabetic treatment for Type 2 diabetes	Januvia	
valganciclovir hydrochloride	Cytomegalovirus treatment	Valcyte, . . .	
bendamustine hydrochloride	Lymphocytic lukemia treatment	Treanda	
fingolimod hydrochloride	Multiple sclerosis treatment	Gilenya	
raltegravir potassium	HIV infection treatment	Isentress	
piperacillin sodium	Extended spectrum antibiotic	Zosyn (1 of 2 APIs)	
vancomycin hydrochloride	Treatment of gram-positive bacterial infections	Vancocin	

* Crystal Structure determined

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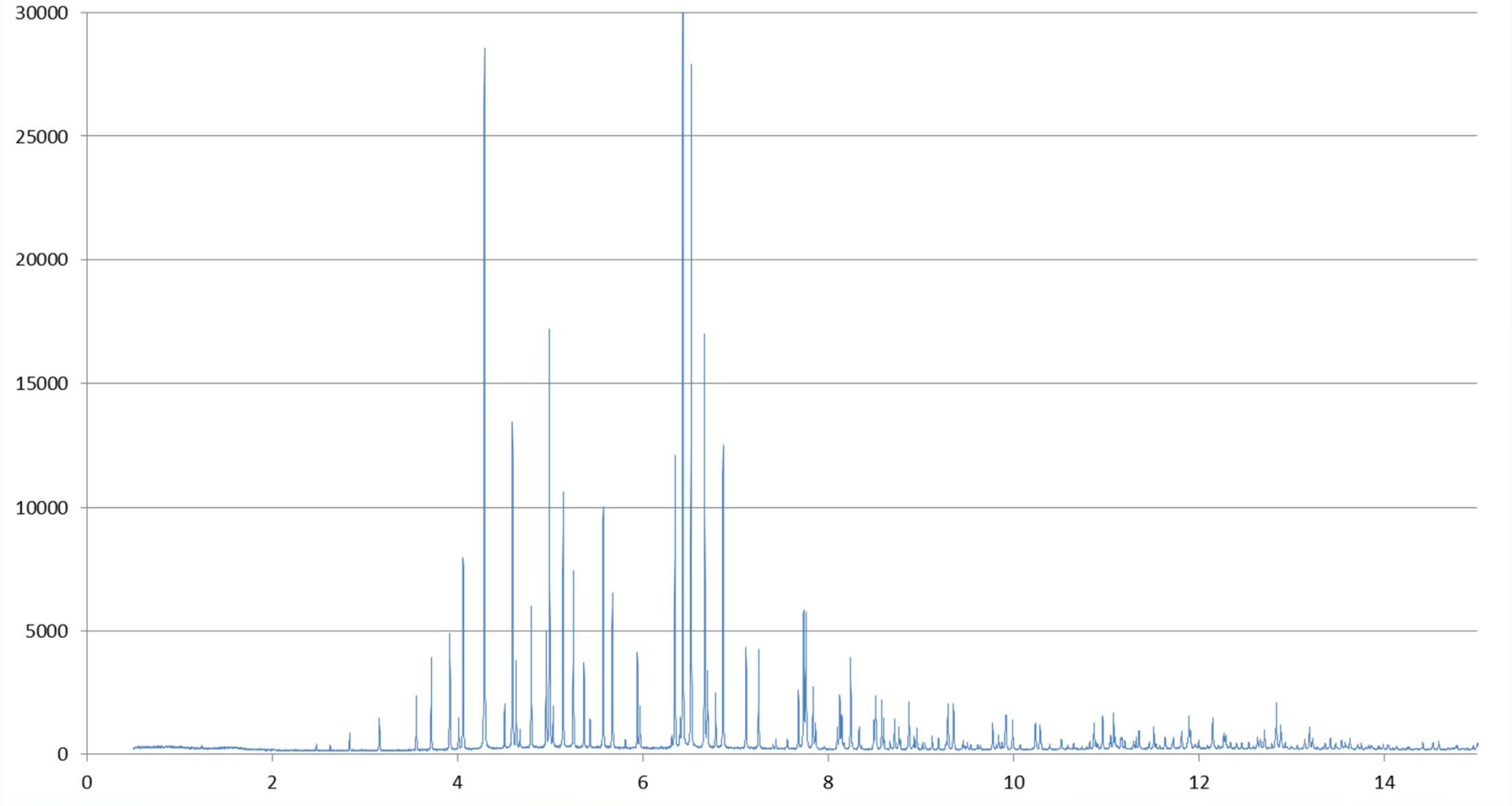
XRPD Data for Sitagliptin Phosphate Monohydrate Collected at APS 11-BM Beamline



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Crystal Structure of Risedronate Sodium Hemipentahydrate

Viewed approximately along the *b*-axis.

C: grey

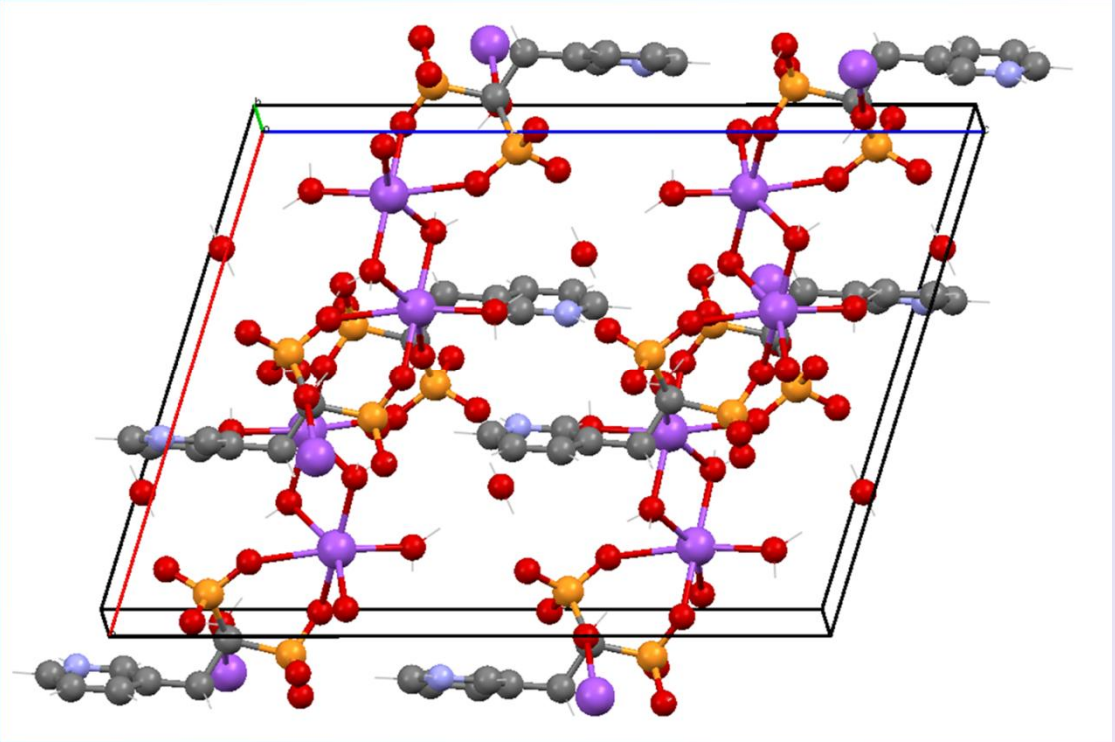
Na: violet

O: red

N: blue

P: orange

H atoms shown as sticks.



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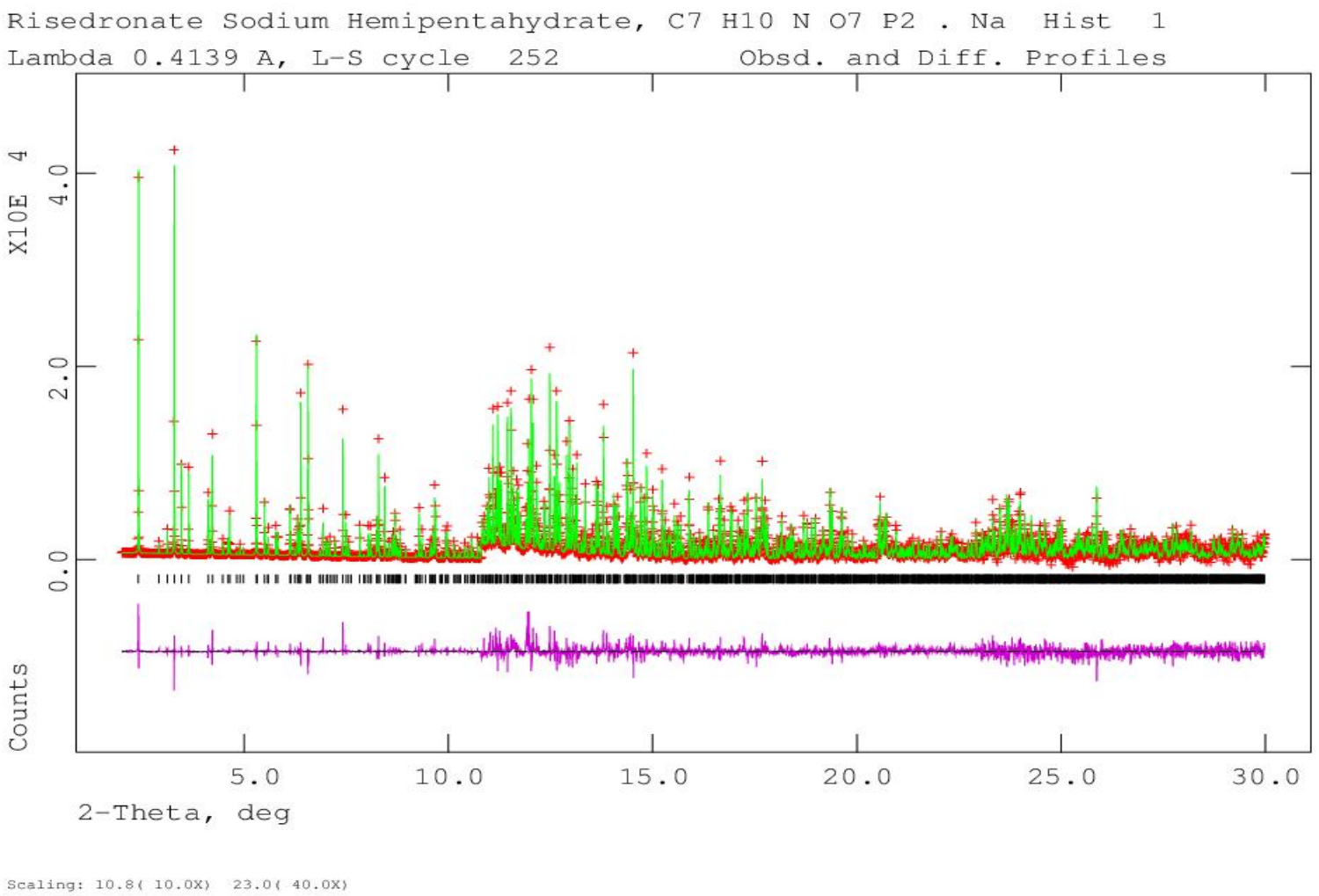
Rietveld Fit for Risedronate Sodium Hemipentahydrate



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Crystal Structure of Levalbuterol HCl

Viewed approximately along the *b*-axis.

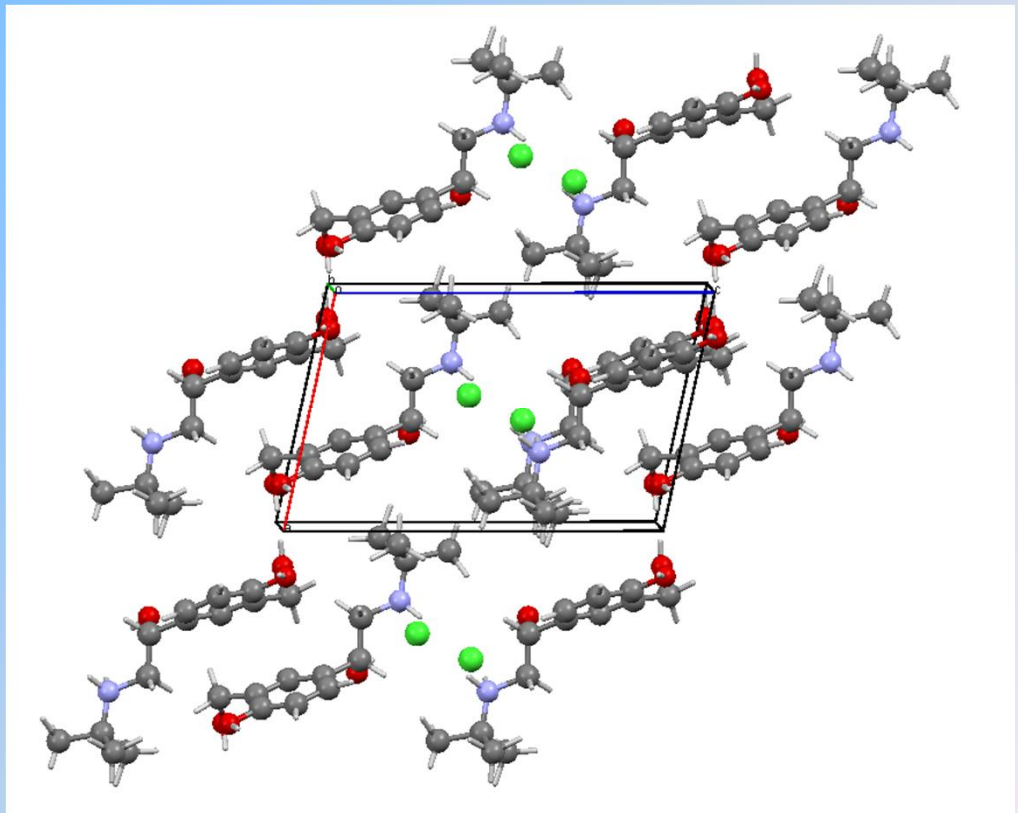
C: grey

O: red

N: blue

Cl: green

H atoms shown as sticks.



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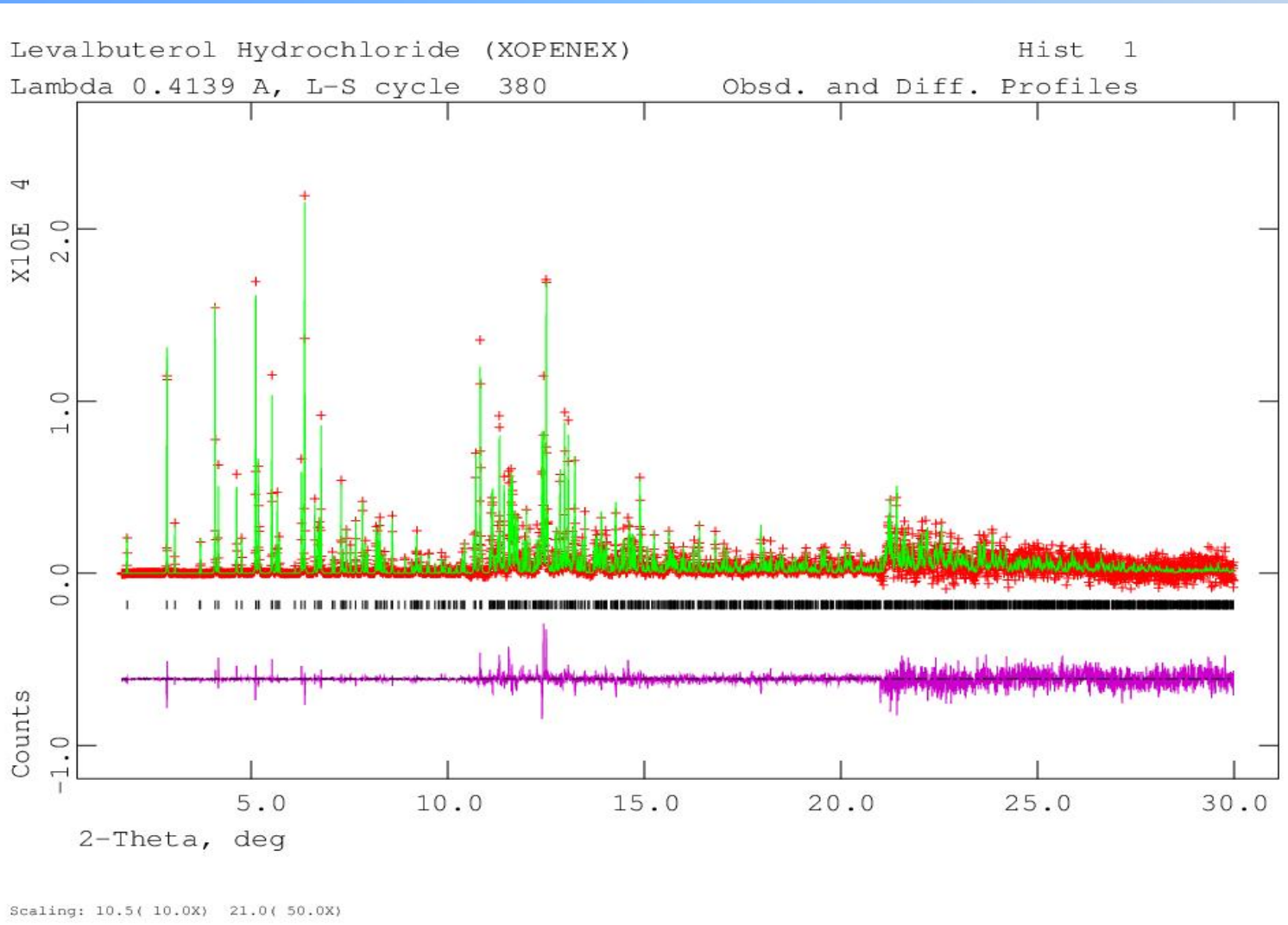
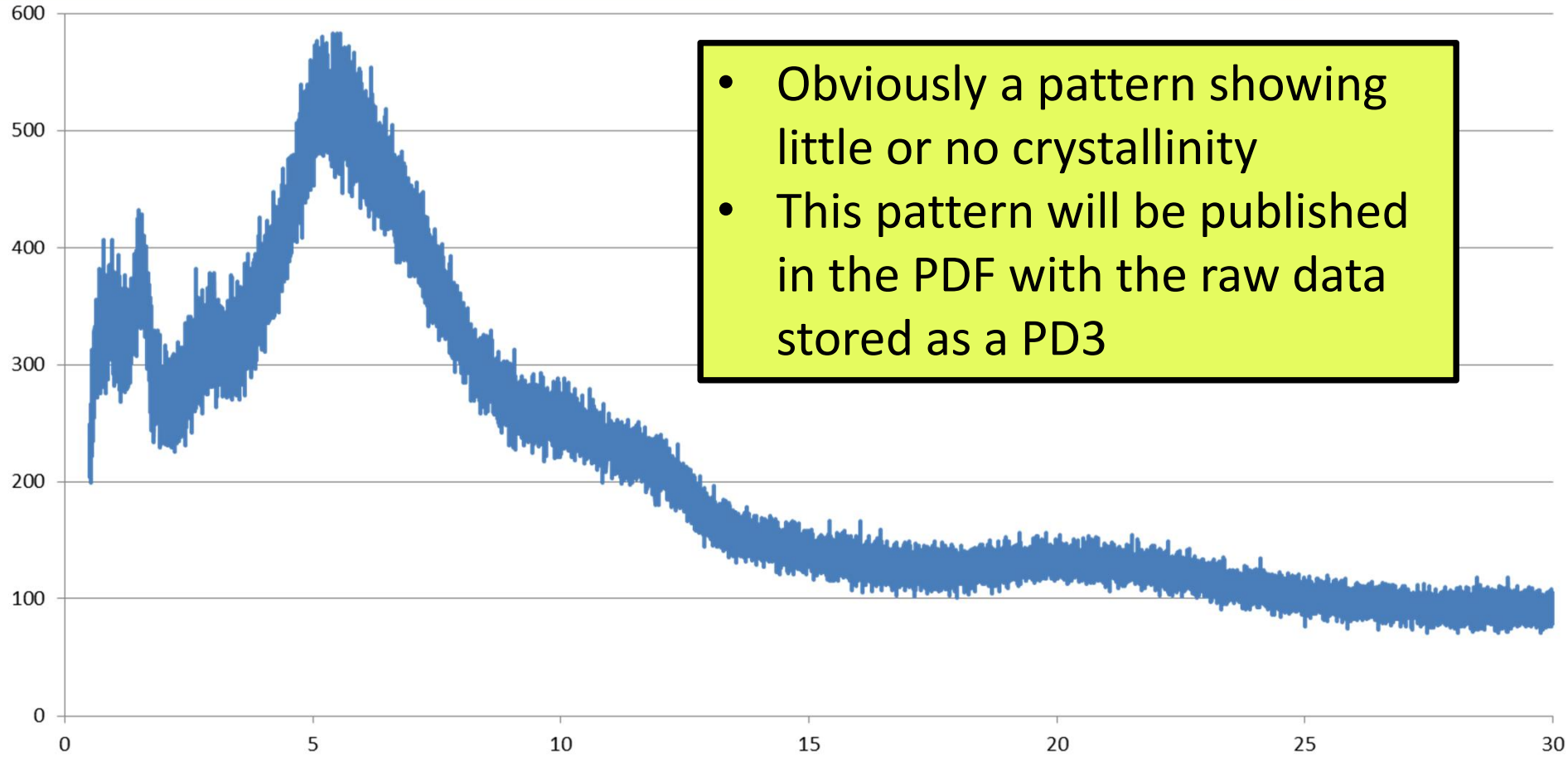
Rietveld fit for Levalbuterol HCl



XRPD Data for Vancomycin HCl Collected at APS 11-BM Beamline



- Obviously a pattern showing little or no crystallinity
- This pattern will be published in the PDF with the raw data stored as a PD3

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Conclusions

- Data for 16 materials have already been obtained for processing and inclusion in the PDF-4+/Organics 2015 database.
- Four structures have been determined from high-quality synchrotron powder diffraction data.
- Beamtime has been approved for the remaining 47 APIs – 18 of these have already been obtained as powders from various sources.

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