Industry-University Partnerships at a DOE facility: One Academic's View

Peter Stephens
Stony Brook University

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Access to NSLS is by:

- Participating Research Team (investment by investigators).
- General User Proposal (requires peer review, scheduling can take several months).
- Proprietary Usage. Only safety review, no obligation to publish.

Examples from pharmaceutical industry, especially patent litigation.

These images are merely visual aids which accompanied a verbal presentation.

Note: data and interpretation here are mine alone, and should not be imputed to any other party.

To use DOE facilities for proprietary work, one must pay cost recovery.
(To whom?)

NSLS. ~$30M/year operating budget. ~60 beamlines. ~5000 hrs/year.
Works out to about $100/hour.

Other costs of operating the beamline?

Who owns the data?

Current policy appears to give the US Government partial ownership of any intellectual property which is reduced to practice at the facility.

NSLS beamline X16C specializes in high resolution powder diffraction; it is currently operated by Stony Brook University which has a proprietary usage agreement.

This allows me to collect proprietary data with very flexible scheduling.

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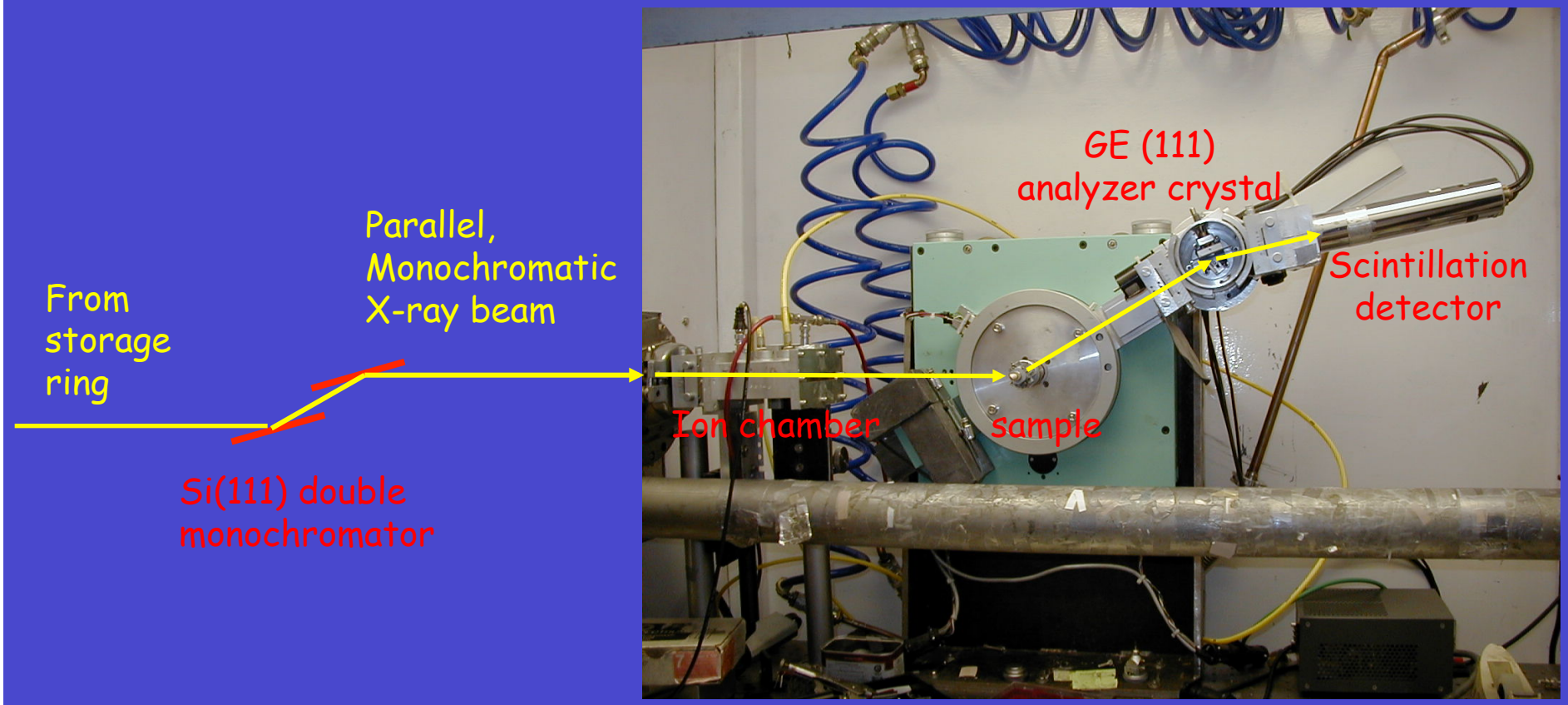

Powder diffraction station at X16C beamline,
National Synchrotron Light Source,
Brookhaven National Laboratory, U. S. A.
(available for general users, rent, or collaboration)

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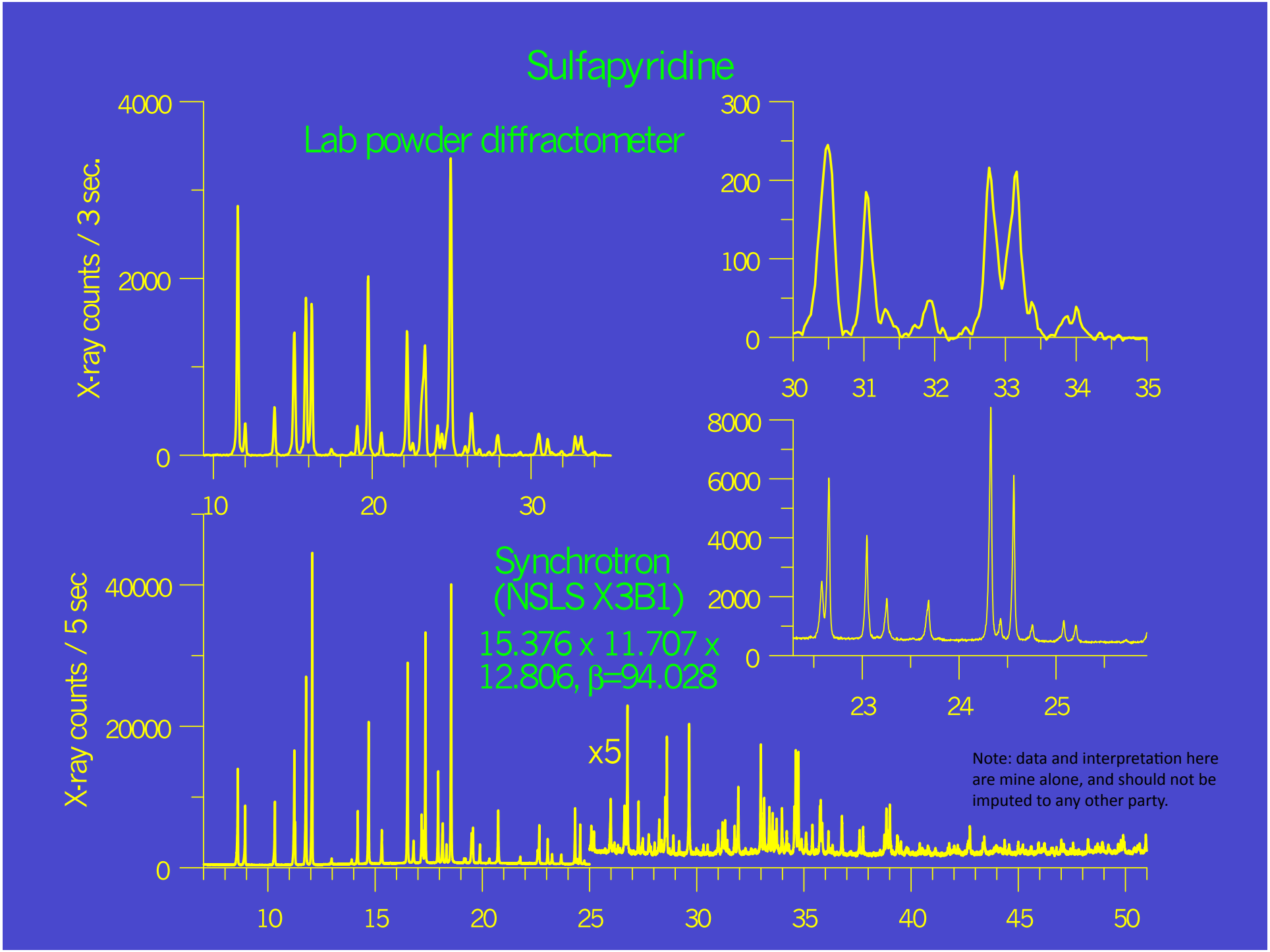
Sulfapyridine
Lab powder diffractometer
X-ray counts / 3 sec.
4000
2000
0
10
20
30
300
200
100
0
30
31
32
33
34
35
8000
6000
4000
2000
0
23
24
25
Synchrotron
(NSLS X3B1)
15.376 x 11.707 x
12.806, β=94.028
X-ray counts / 5 sec
40000
20000
0
x5
10
15
20
25
30
35
40
45
50
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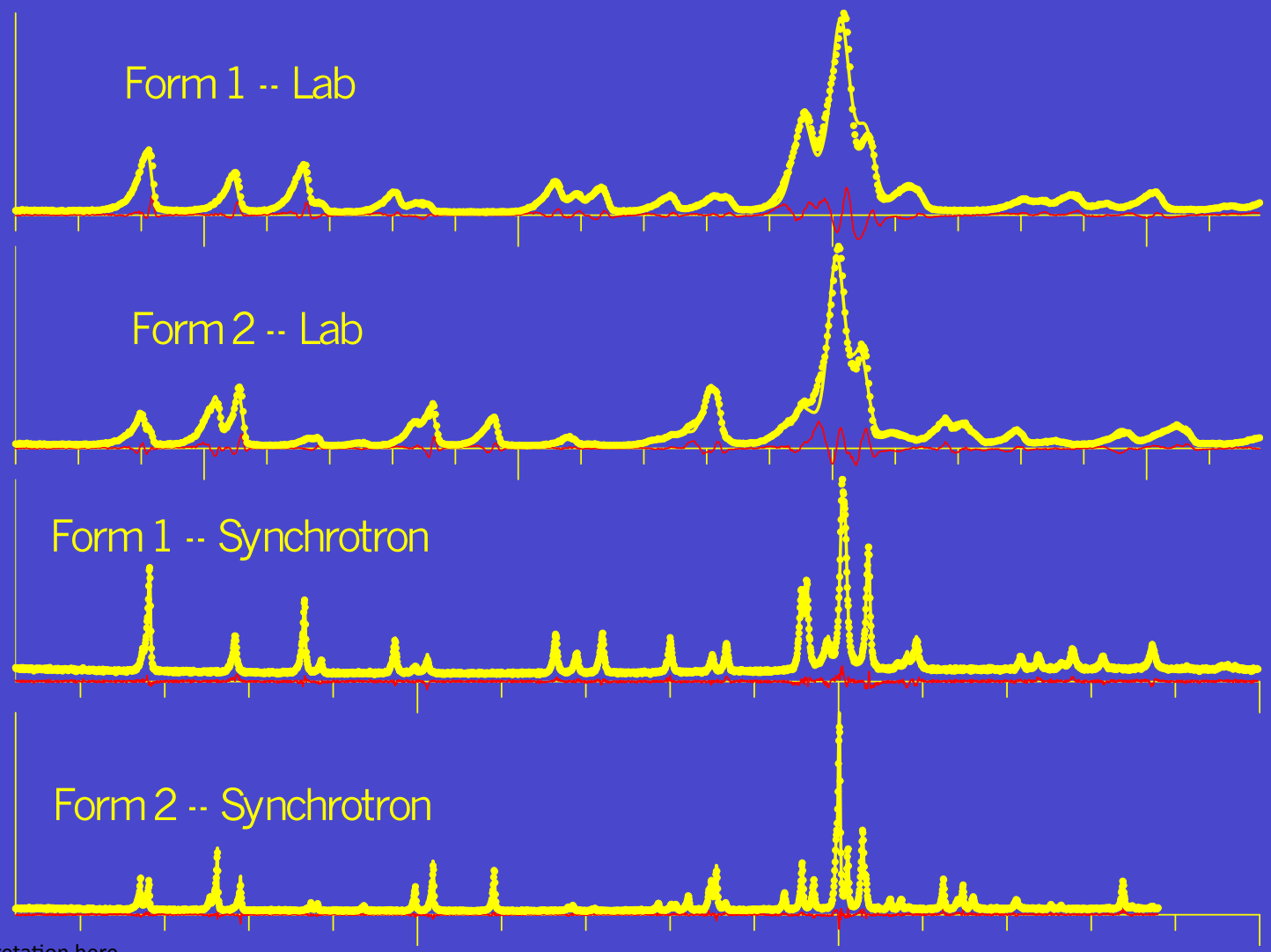
This drug has two polymorphs that can't be quantified except by Rietveld. Compare lab vs. synchrotron data sets.



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Pharmaceutical polymorphs.

Original Ranitidine HCl (‘658) patent expired in 1995

1985. Glaxo obtained ‘431 patent, “a novel form of ranitidine hydrochloride, designated Form 2, having favourable filtration and drying characteristics, characterized by IR and/or X-ray …”

In 1991, Zantac was selling $3.5 Billion / year

In 1991, Novopharm filed ANDA to market RHCl. Admitted it infringed ‘431, but argued it was invalid since they couldn’t produce Form I.

Glaxo won, with <u>much</u> effort expended (1993) to reproduce form I.

Court found that any Form 2 material constituted infringment.

Eventually, ~1997, Novopharm produced pure form I.

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United States Patent [19]
Price et al.

[11] **4,128,658**
[45] **Dec. 5, 1978**

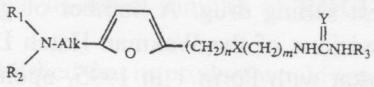
[54] **AMINOALKYL FURAN DERIVATIVES**

[75] Inventors: **Barry J. Price**, Hertford; **John W. Clitherow**, Sawbridgeworth; **John Bradshaw**, Ware, all of England

[73] Assignee: **Allen & Hanburys Limited**, London, England

[21] Appl. No.: **818,762**

[22] Filed: **Jul. 25, 1977**



(I)

and physiologically acceptable salts thereof and N-oxides and hydrates, in which R_1 and R_2 which may be the same or different represent hydrogen, lower alkyl, cycloalkyl, lower alkenyl, aralkyl or lower alkyl interrupted by an oxygen atom or a group

EXAMPLE 32

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine hydrochloride

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine (50 g, 0.16 mole) was dissolved in industrial methylated spirit 74° o.p. (200 ml) containing 0.16 of an equivalent of hydrogen chloride. Ethyl acetate (200 ml) was added slowly to the solution. The hydrochloride crystallised and was filtered off, washed with a mixture of industrial methylated spirit 74° o.p. (50 ml) and ethyl acetate (50 ml) and was dried at 50°. The product (50 g) was obtained as an off-white solid m.p. 133°–134°.

powder diffraction pattern expressed in terms of "d" spacings and relative intensities (I) (s=strong, m=medium, w=weak, v=very, d=diffuse) and obtained by the Debye Scherrer method in a 114.6 mm diameter camera by exposure for 12 hours to CoK_α radiation and for 3 hours to CuKa radiation:

d (Å)	I	d (Å)	I
10.73	m	3.40	2 w
6.50	3 vwd	3.35	2 vwd
6.13	m	3.25	wd
5.83	s	3.12	2 vw
5.63	3 vwd	3.04	2 vwd
5.42	s	2.97	3 vwd
5.06	2 vw	2.93	3 vwd
4.92	w	2.88	3 vwd
4.59	2 vw	2.81	vwd
4.40	s	2.72	vwd
4.28	w	2.66	3 vwd
3.91	wd	2.47	2 vwd
3.79	s	2.44	vw
3.71	m	2.34	2 vwd
3.60	vwd	2.30	3 vwd
3.46	m	2.21	2 vwd

3. A pharmaceutical composition in the form of tablets comprising Form 2 ranitidine hydrochloride as defined in claim 1 together with at least one inert pharamceutically acceptable carrier or diluent.

4. A pharmaceutical composition in the form of tablets comprising Form 2 ranitidine hydrochloride as defined in claim 2 together with at least one inert pharmaceutically acceptable carrier or diluent.

5. A pharmaceutical composition in the form of capsules comprising Form 2 ranitidine hydrochloride as defined in claim 1 together with at least one inert pharmaceutically acceptable carrier or diluent.

6. A pharmaceutical composition in the form of capsules comprising Form 2 ranitidine hydrochloride as defined in claim 2 together with at least one inert pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition in the form of a powder comprising Form 2 ranitidine hydrochloride as defined in claim 1 together with at least one inert pharmaceutically acceptable carrier or diluent.

8. A p
powder c
defined in
maceutica
9. A p
lozenges
as define
pharmace
10. A
lozenges
as define
pharmace
11. A
supposito
ride as de
pharmace
12. A
supposito
ride as de
pharmace
13. A
retention
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14. A
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18. A
histamine
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claimed i

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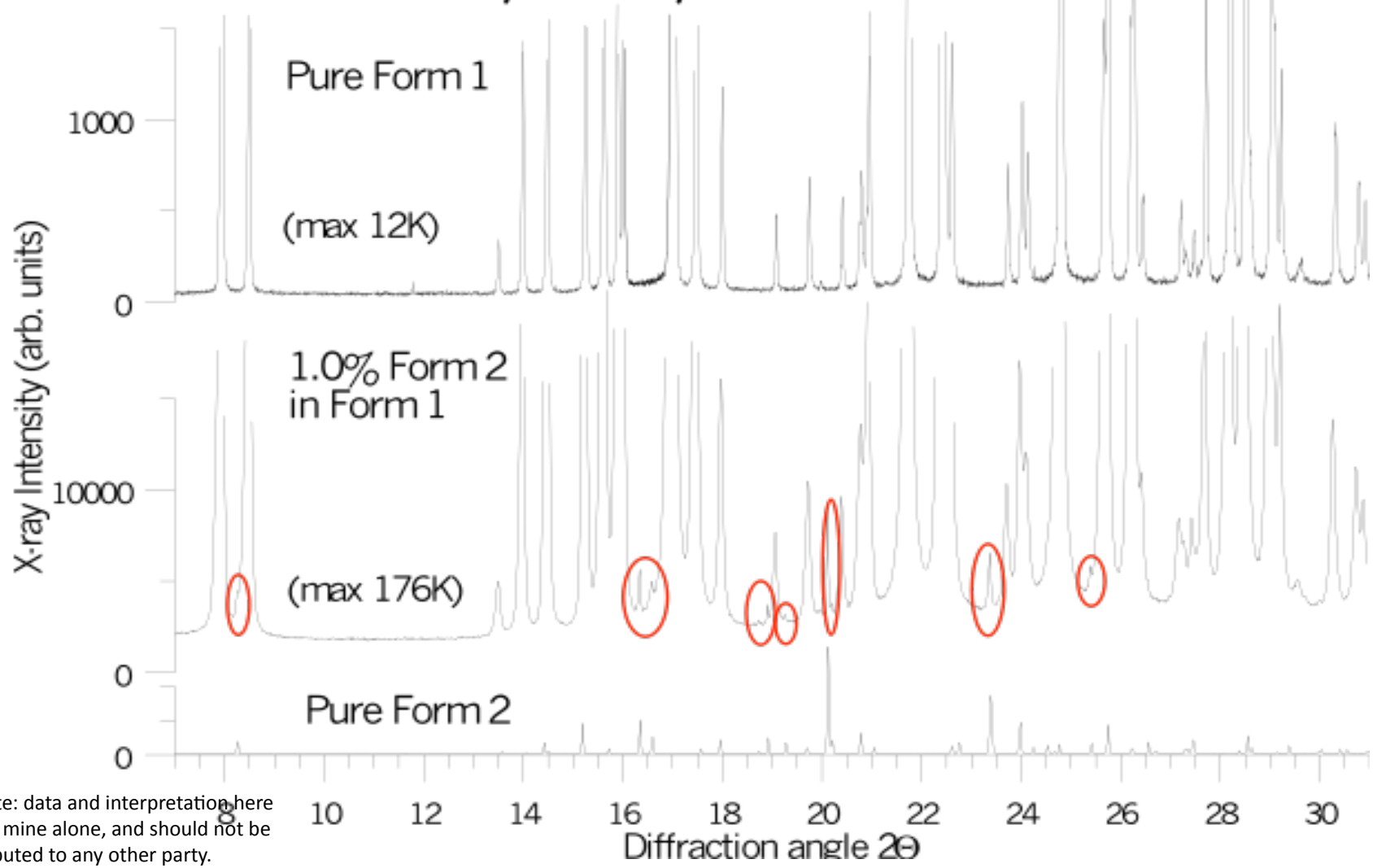
Detection sensitivity depends on
signal intensity
sharp peaks
low background
All are enhanced by use of synchrotron radiation

Two polymorphs of Zantac®, ranitidine hydrochloride



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Abbott Laboratories is the exclusive licensee of US patent 4,935,507 for crystalline cefdinir anhydrate. That patent describes a process to produce anhydrate, claimed by seven powder X-ray diffraction peaks.

What we claim is:

1. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem.-4-carboxylic acid (syn isomer) which shows the peaks at the diffraction angles shown in the following table in its powder X-ray diffraction pattern:

diffraction angle(°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.5
about 28.1

In 2007, several generic manufacturers announced intent to sell cefdinir (Hatch-Waxman), and were promptly sued for infringement.

Is the subject monohydrate pure, or does it contain the patented anhydrate?

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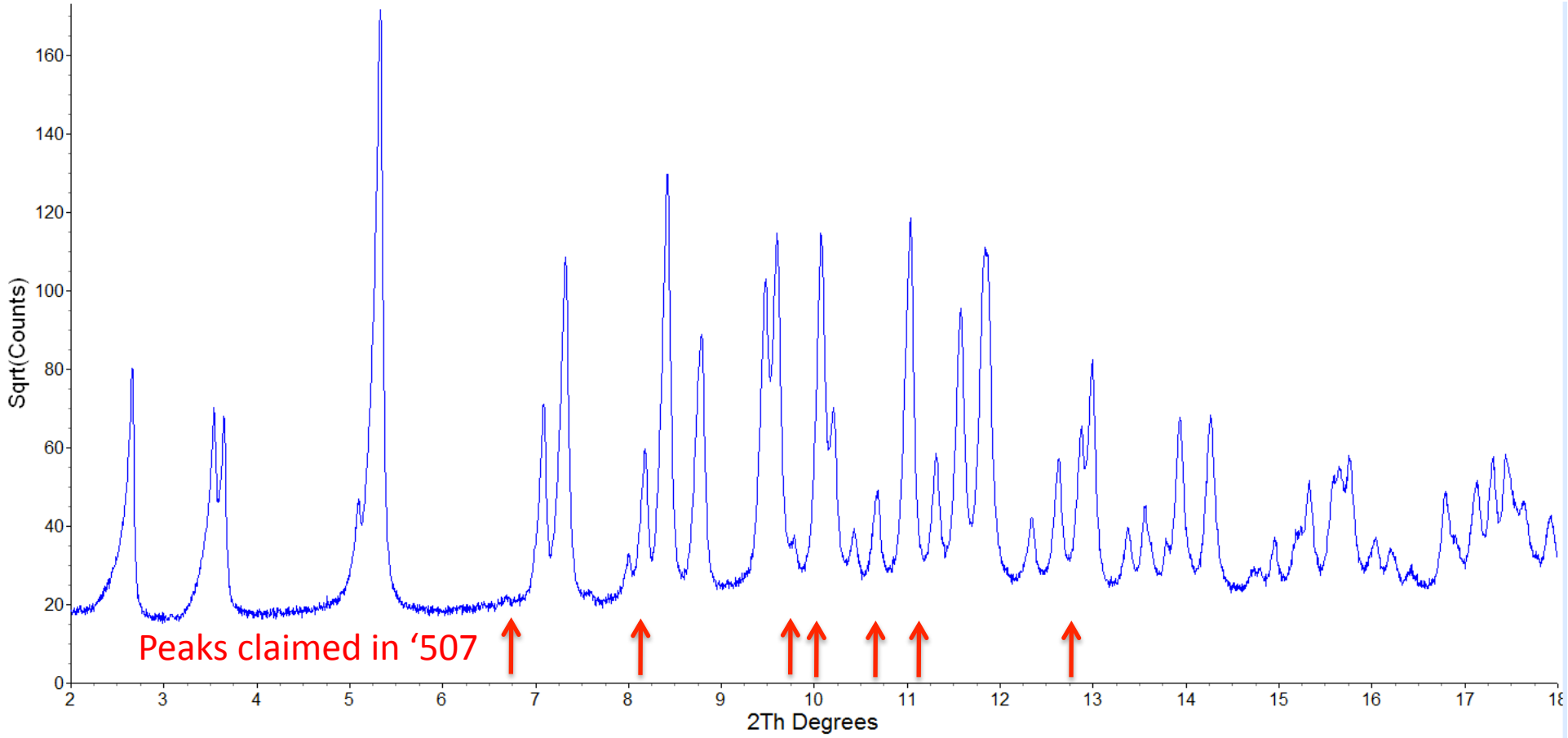
Is the subject monohydrate pure, or does it contain the patented anhydrate?



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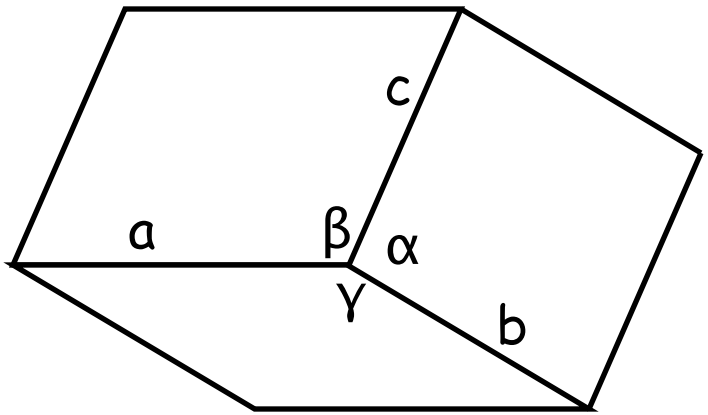
Any crystalline material is characterized by its lattice.



The lattice dimensions (lattice parameters) govern the position of all possible diffraction peaks.

Knowing lattice dimensions allows one to calculate the position of every (*hkl*) peak. With good data, one can go the other way and determine the lattice from powder peak positions.

The math is a bit tedious, but the problem is to find *A,B,…,F* such that every peak can be assigned (*h,k,l*) so that its position is given by this equation.

$$\frac{4\sin^2\theta}{\lambda^2} = 1/d^2 = Ah^2 + Bk^2 + Cl^2 + Dkl + Ehl + Fkl$$

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High-resolution PXRD data indexes to an orthorhombic lattice, probably $C222_1$, with dimensions a = 44.950 Å, b = 15.8495 Å, c = 4.996 Å.

Pawley fit (no information about atomic positions – refine only peak shapes and lattice dimensions) fit to the experimental data.

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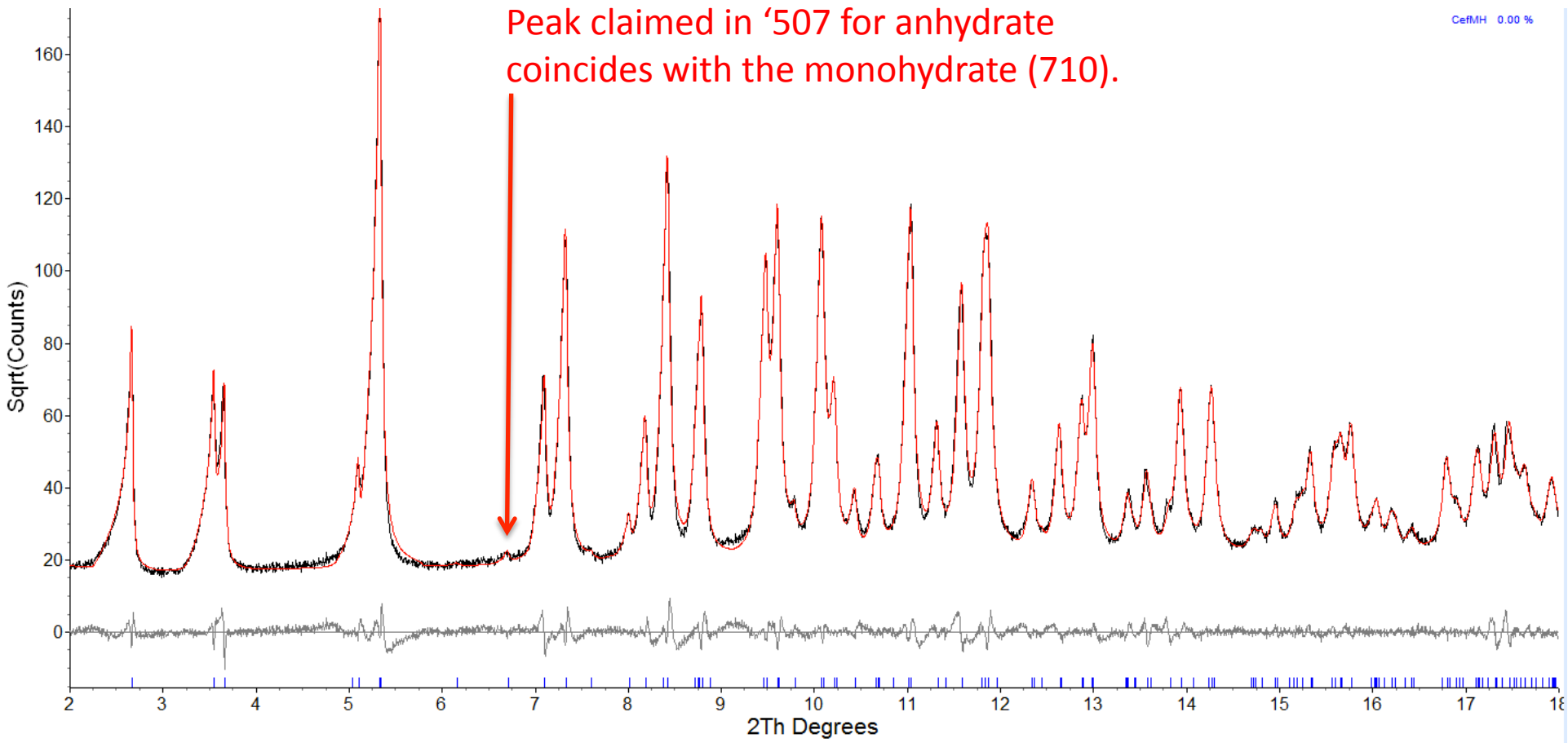

Real business problem:
_____ has a patented polymorph of _____ , and suspects that _____ is selling material that infringes. It is desired to examine the commercial tablets and determine the polymorph of the API for potential litigation.

Proxy:
Examine commercial tablet of Endocet 500/7.5
Gross tablet 607 mg
Acetaminophen 500 mg – known lattice & structure
Oxycodone (as HCl) 7.5 mg – pattern in PDF but lattice unknown,*

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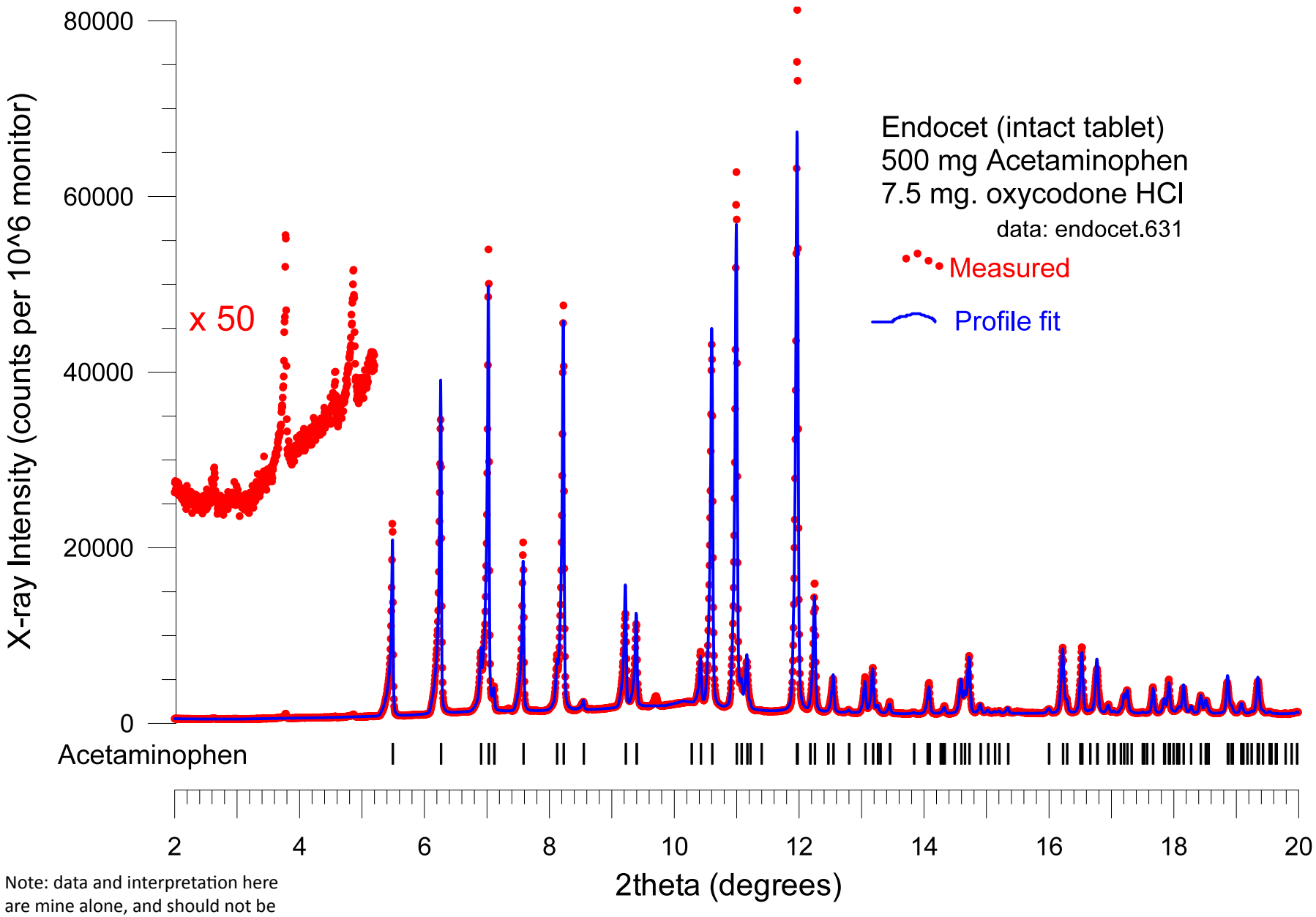

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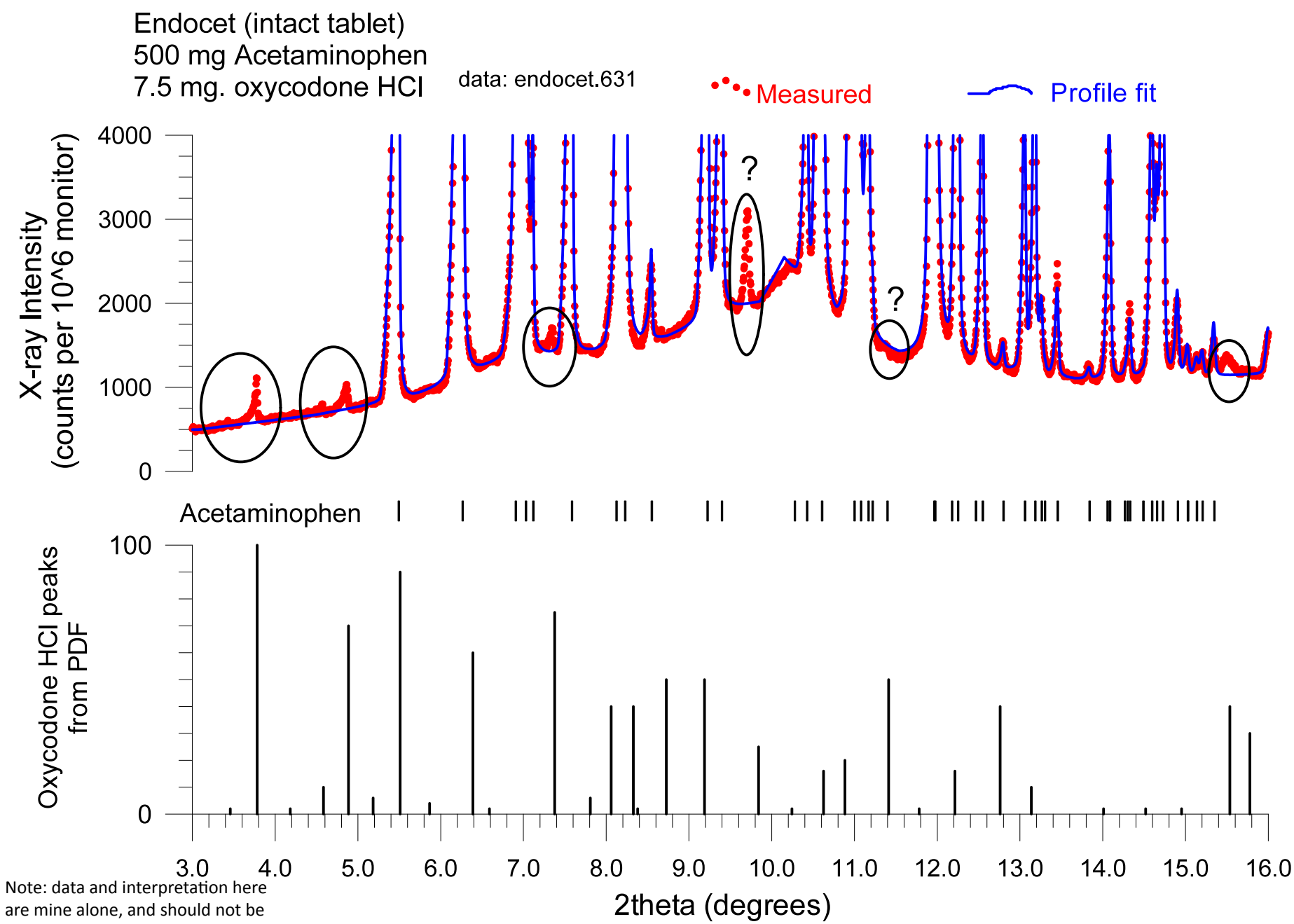

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