

ERF

**Technology Transfer and Industrial Relations
in Research Infrastructures**

Trieste, Italy, 6-7 June 2013

**The Collaboration between Elettra
Sincrotrone Trieste and Zambon
Chemicals on Polymorphs
Characterization**

**Zach – Zambon Chemicals
and
Elettra Sincrotrone Trieste**

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1906

ZaCh System



| | |
|-------------------------|------------------------|
| Total area | 260.000 m ² |
| Plant area | 100.000 m ² |
| Buildings | 30.000 m ² |
| Production capacity | 900 m ³ |
| Reactors capacity | 2-17 m ³ |
| Total handled mat /year | 1.500 MT |
| R&D Staff | 32 |
| QA/QC Staff | 40 |

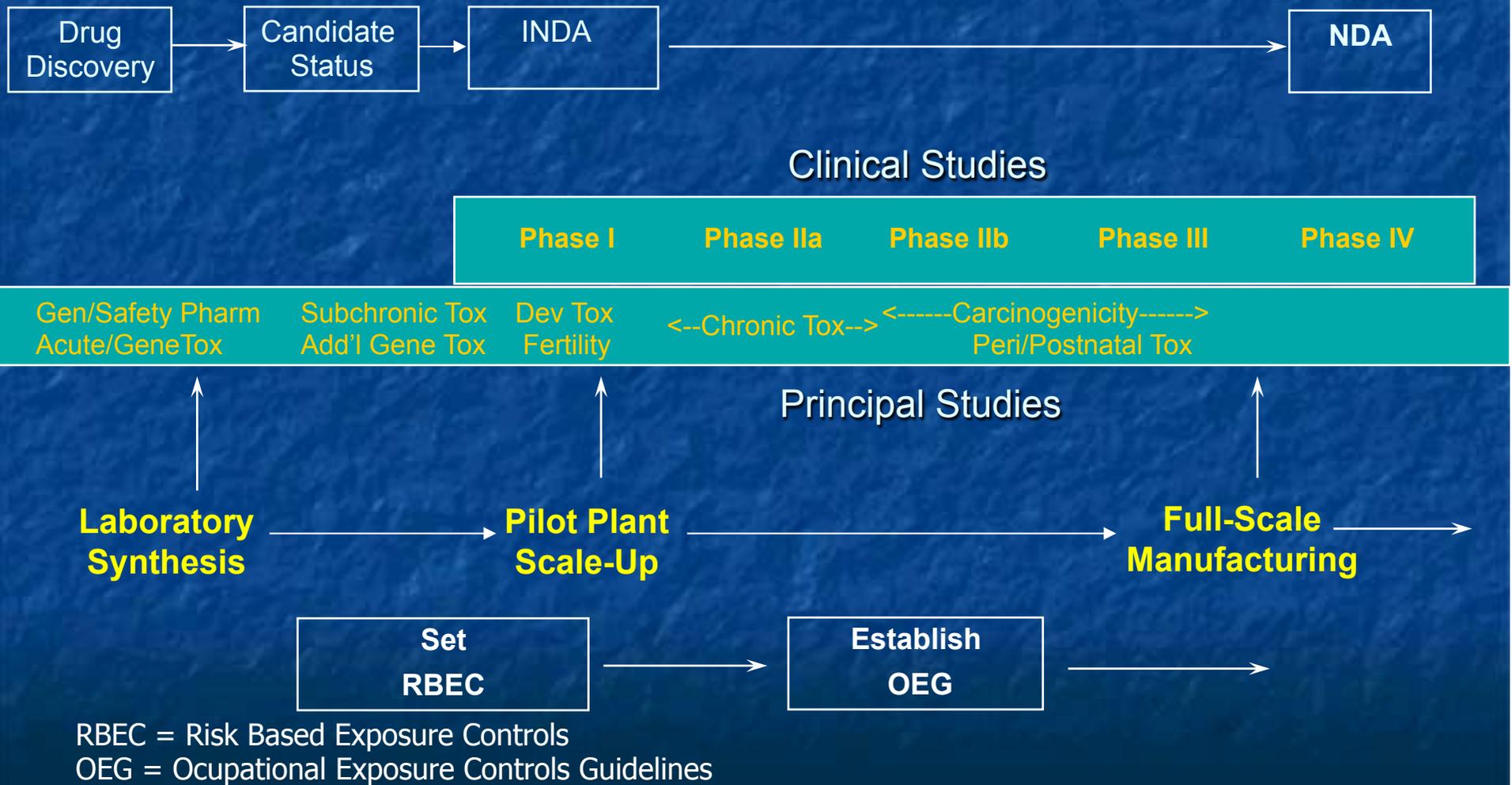


Project History

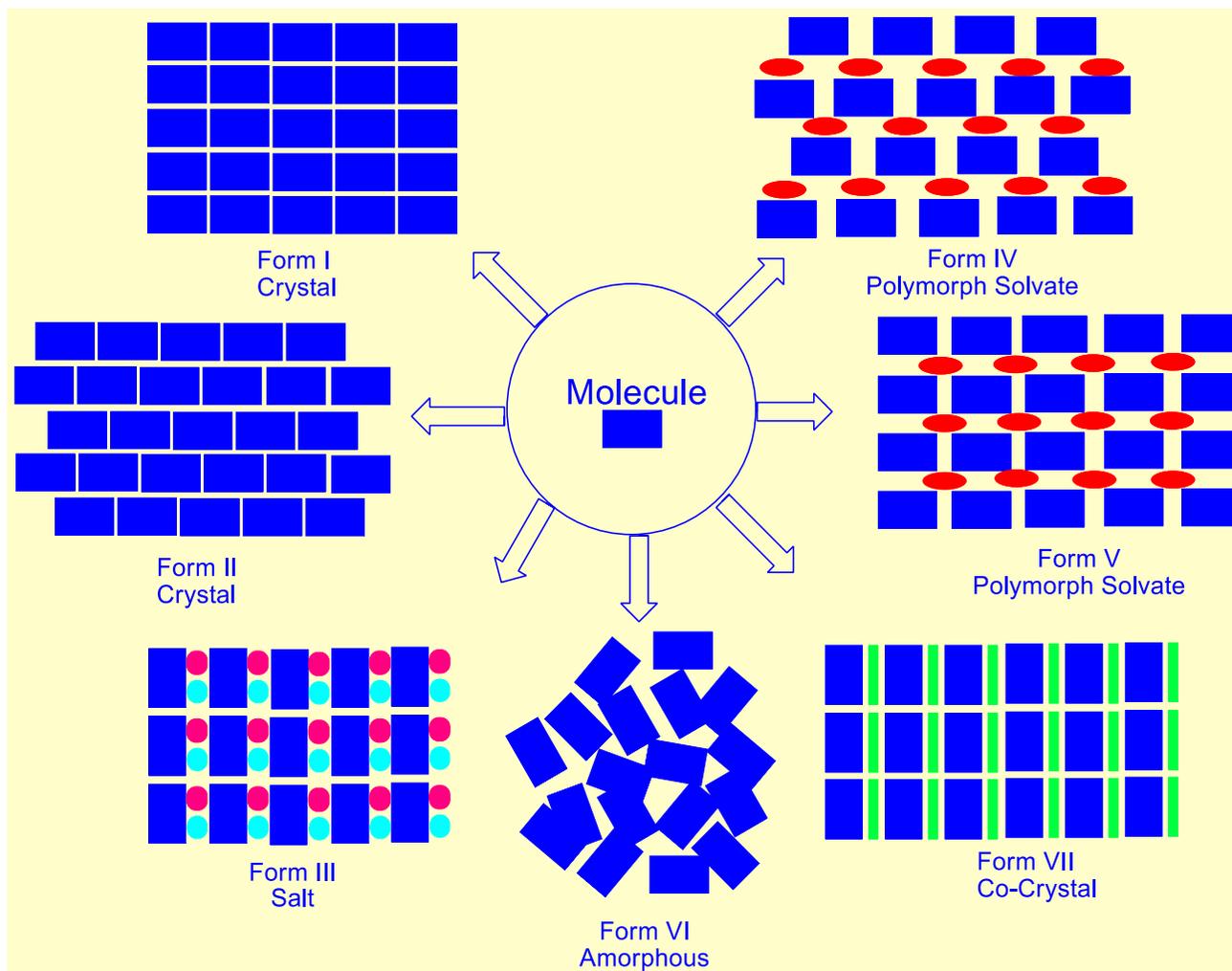
- 2008 Zach Visit at the Synchrotron Facility
- 2009 Project Definition
- 2009 The Agreement
- 2010 Case Studies Development
- 2012 Patent Application and Typical Project/Protocol Structure
- 2013 Development of more complex projects



TIMELINE FOR DRUG DEVELOPMENT

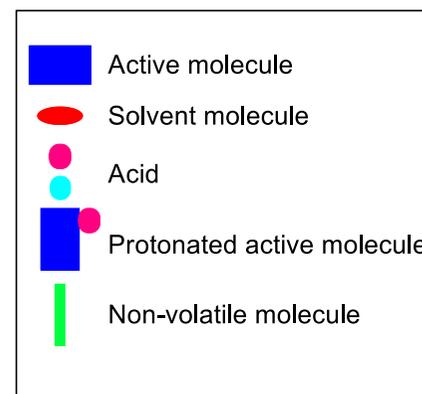


Structural Relationship Between “True” Polymorphs, Solvates, Polymorphs of Solvates and the Amorphous Phase



Drug Substance:
therapeutic moiety
(solvate, salt or co-
crystal)

Active molecule:
single, uncharged
molecule



D. Braga and F. Grepioni, *Making Crystals by Design*, Wiley-VCH 2007, p 294 and R. Hilfiker (ed), *Polymorphism in the Pharmaceutical Industry*, Wiley-VCH, 2006, p 2

Characterization of Polymorphs

- Polarizing optical microscopy and thermomicroscopy
- Thermal analysis procedures, DSC, TGA
- NMR, infrared absorption and Raman spectroscopy

“It should be emphasized that the definitive criterion for the existence of polymorphism is via demonstration of a nonequivalent crystal structure, usually by comparison of the x-ray diffraction patterns” *

New analytical technologies, and modifications to existing technology, are continually being developed.

Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

It is generally technically very difficult to measure polymorphic changes in drug products.

FDA: Background Information for the October 2002 ACPS Meeting Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications

The Commencement is the Most Important Part of the Work

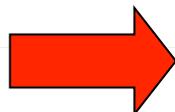


Business started with...Regulatory and Quality Compliance

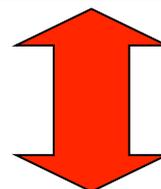
- Elettra - Sincrotrone Trieste S.C.p.A. is a multidisciplinary international laboratory of excellence, specialized in generating high quality synchrotron and free-electron laser light and applying it in materials science. The team at Trieste is highly respected
- The data produced is of required quality
- Zach have installed a cGMP documentation system
- Zach has carried out an internal audit of the facility to ensure its cGMP compliance and validation of the systems

Who provides what and project management

Client provides:
Project data and samples
where possible



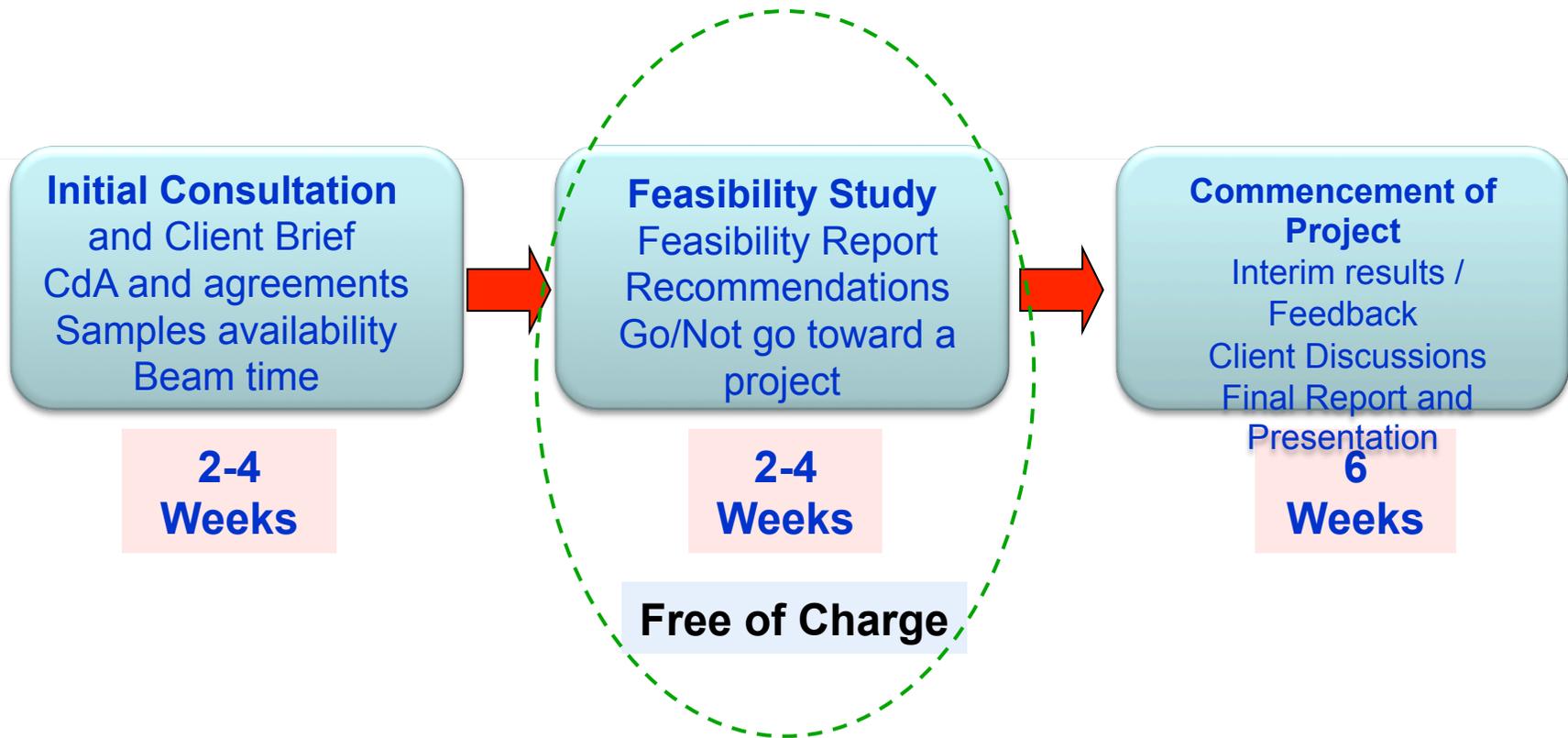
Zach provides:
Project management and communication
Samples/physical forms for evaluation and
to enable the quantitation, as required
Presentation of the results in a conventional
format with data interpretation
Final project report and recommendations



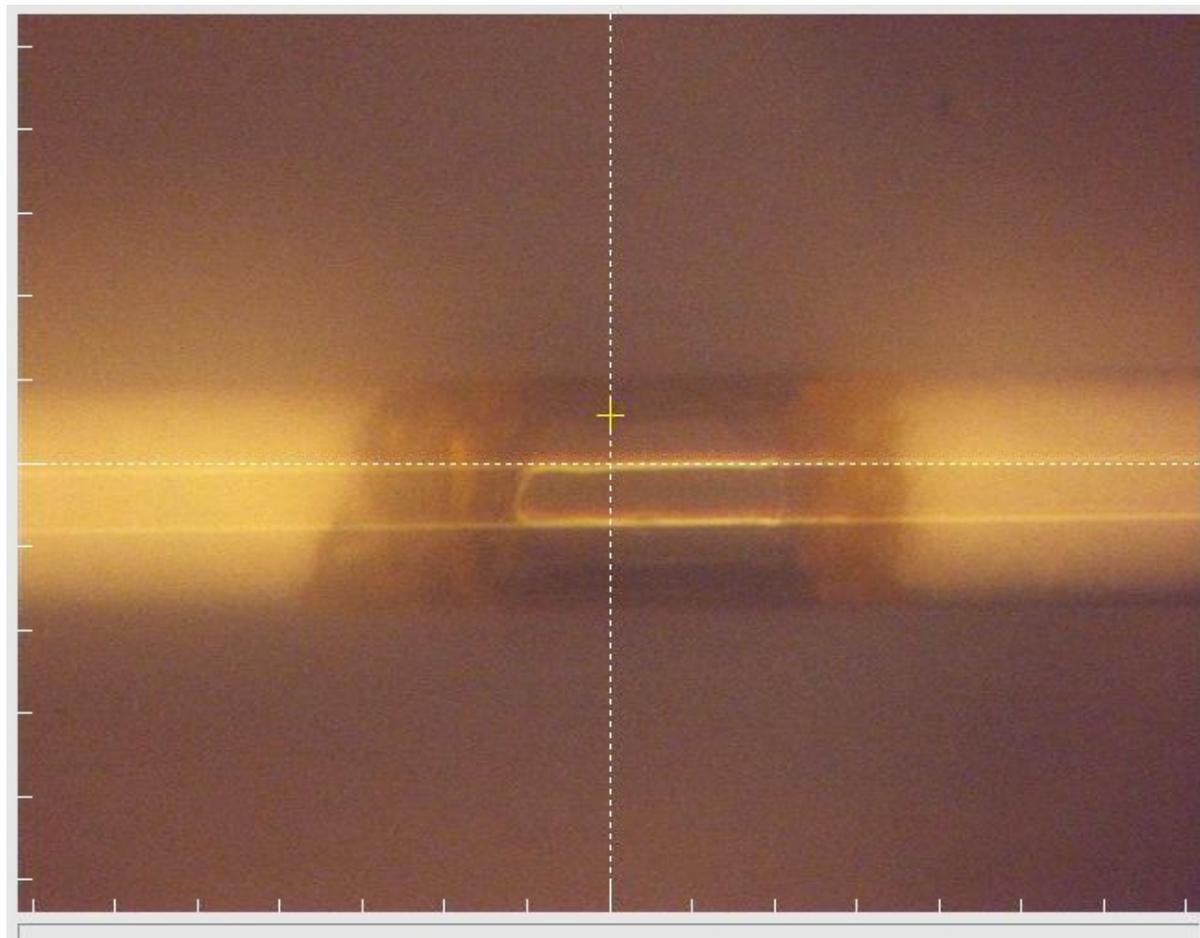
**Elettra Sincrotrone
provides:**
Synchrotron beam time
and expertise, data
elaboration



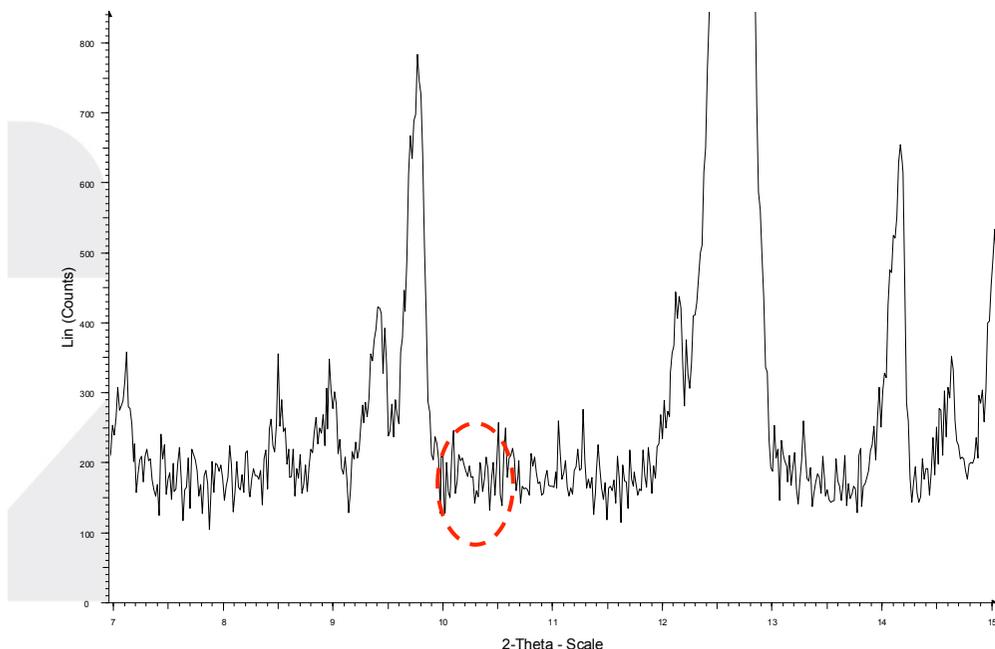
Project structure



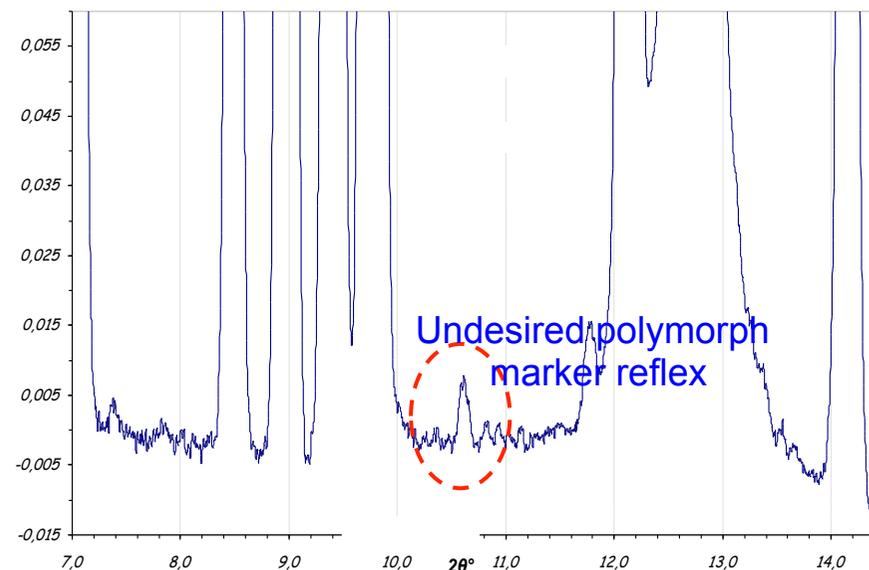
First Trial – A Failure



Case # 5 Synchrotron Radiation for Seed Quality Assessment and Control



Conventional XRPD
Bruker D8 Advance Instrument
No Evidence of Contamination



Synchrotron Radiation XR-PD
Evidence of Contamination

D8 Advance (Bruker XRPD): Scan 3-40° 2θ, source Cu, 50mA, 35kV, Radiations K(α1) e K(α2), Primary optics: divergence slit 0,3°, sollar of 2,5°, Secondary optics: Ni Filter, 0,5mm, Soller 1,5° Sample-det dist 217mm; Detector: PSD detector (LynxEye, Bruker), operative cond: scan step size 0,015°, count time 0,5s and PSD window 0,8°, Rotative Autosampler 25 x 1 mm

The Patent Application

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SI, SM, ST, SV, SY, TH, TI, TM, TN, TR

(54) Title: METHOD OF DETECTING POLYMORPHS USING SYNCHROTRON RADIATION

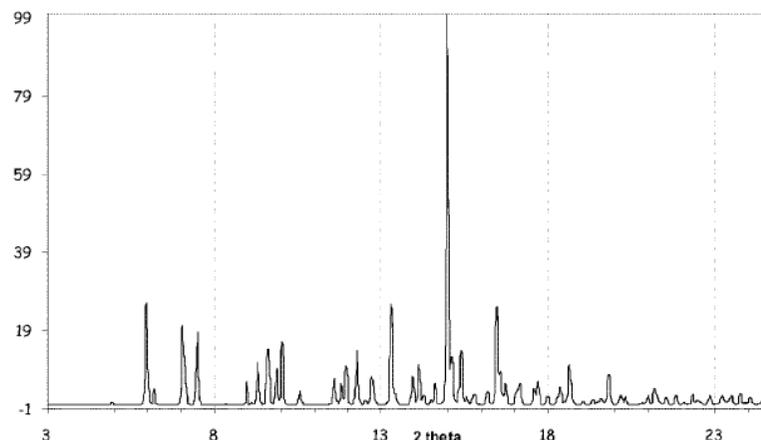


Fig. 7.a (1.0Å)

(57) Abstract: A method of detecting polymorphs using X-ray produced by a synchrotron source is described. In particular, the method allows to detect particular polymorphs present in small amounts in mixtures of polymorphic compounds present in a prevailing amount. The method offers a powerful resolution of mixtures of polymorph and finds application particularly in the pharmaceutical field.



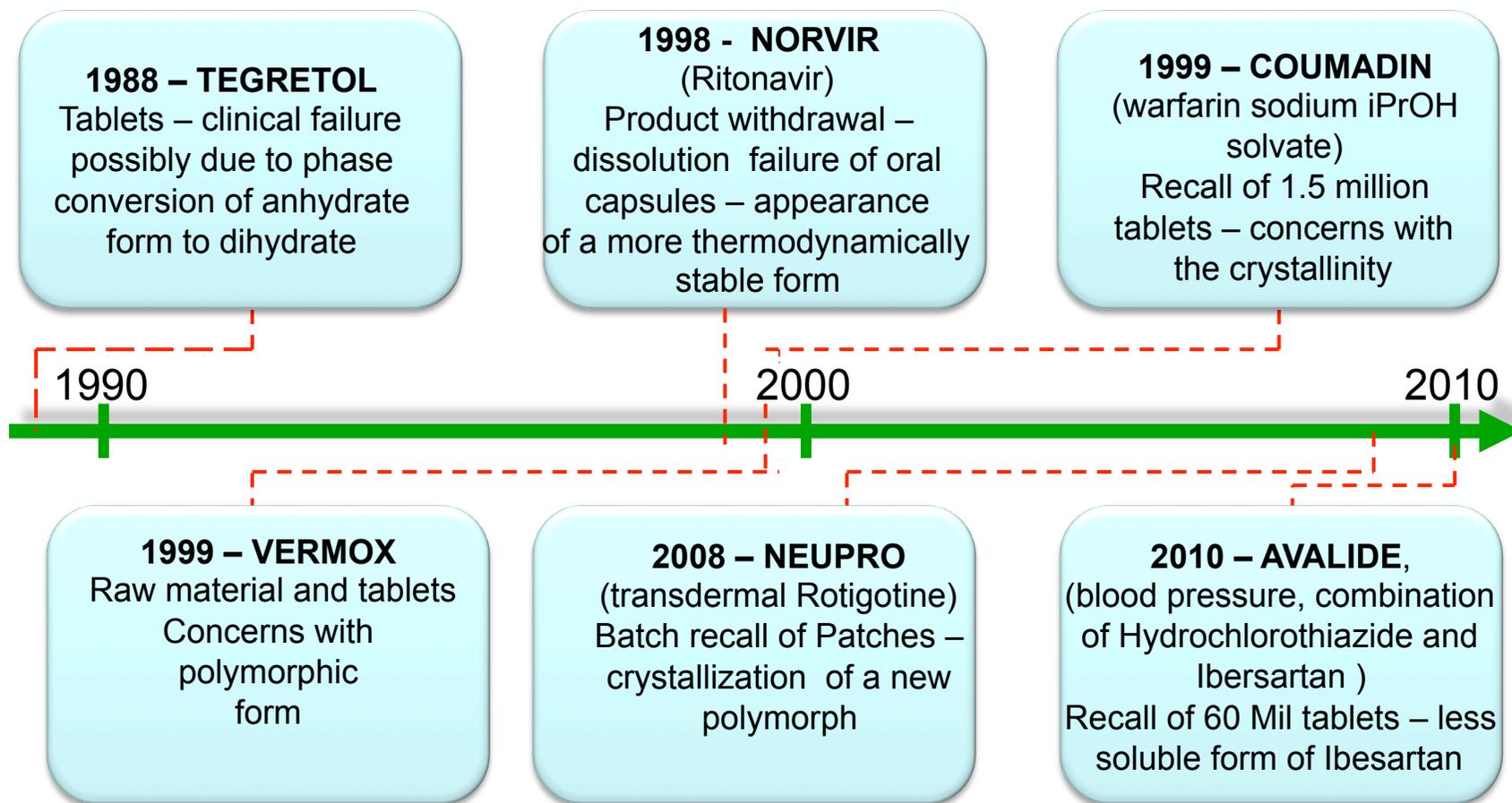
WO 2012/156450 A2

Top Best Selling Small – Molecule Drugs

A. Y. Lee, D. Erdemir and A. S. Myerson, *Annu. Rev. Chem. Biomol. Eng.* 2011, 2:259–80

| Rank | Brand Name | Companies | API | Indication | Sales (\$ bill) | Min n. of solid phases |
|------|------------|------------------------|--|----------------------|-----------------|------------------------|
| 1 | Lipitor | Pfizer, Astellas | Atorvastatin Calcium | High LDL cholesterol | 12,5 | 41 |
| 2 | Plavix | BMS, Sanofi Aventis | Clopidogrel bisulfate | Atherosclerosis | 9,3 | 6 |
| 3 | Advair | Glaxo SmithKline | Fluticasone propionate Salmeterol xinafoate | Asthma | 7,8 | 2 2 |
| 4 | Diovan | Novartis | Valsartan | Hypertension | 6,0 | 10 |
| 5 | Abilify | Otsuka, BMS | Aripiprazole | Schizophrenia | 5,6 | 9 |
| 6 | Nexium | Astra Zeneca | Esomeprazole magnesium | Ulcer | 5,0 | 4 |
| 7 | Zyprexa | Lilly | Olanzapine | Schizophrenia | 4,9 | 25 |
| 8 | Seroquel | Astra Zeneca, Astellas | Quetiapine Fumarate | Schizophrenia | 4,9 | 2 |
| 9 | Crestor | Astra Zeneca, Shinoggi | Rosuvastatin calcium | High LDL cholesterol | 4,7 | 3 |
| 10 | Singulair | Merck | Montelukast sodium | Asthma | 4,7 | 4 |

Solid-state issues with polymorphism of pharmaceutical drugs over the past 25 years



Manufacturing problems hit Abbott's HIV drug ritonavir

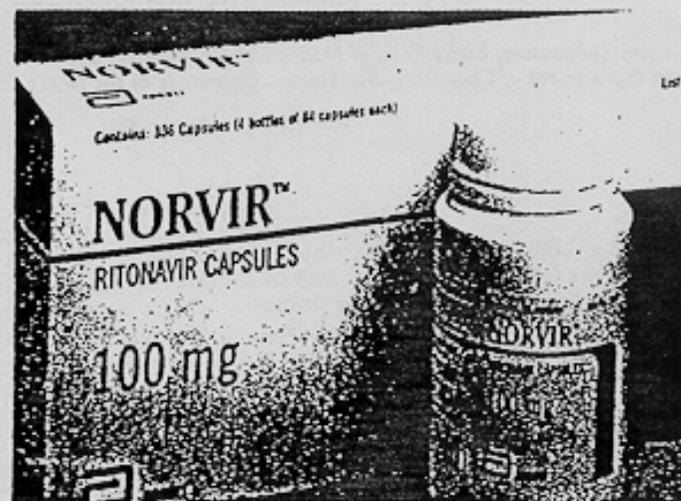
Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

Production of Norvir oral solution is being increased to compensate for the likely capsule shortage. The solution is bioequivalent to the capsule formulation, with the recommended 600mg twice daily dosage of ritonavir corresponding to 7.5ml twice daily of the solution.

There is said to be no problem with the capsules that are already on the market.

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were



Capsules unlikely to be available from mid-August

working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

The vast majority of sales of Norvir are of the capsules rather than the oral solution. The solution is normally more expensive than the capsules but Abbott says that, while the capsules are unavailable, the solution will be sold at the capsule price.

Norvir oral solution has a bitter taste. This can be reduced by mixing with chocolate milk, Abbott says.

The company has set up a helpline (0800 0183340) for patients and health professionals. A letter explaining the situation will be given to health professionals for them to issue to patients if they wish.

FDA enquiry on Ritonavir

Q: *You are a large multinational company. Your scientists are obviously smart. How could this happen?*

A: *A company's size and the collective IQ's of their scientists have no relationship to this problem...*

.... There are many **misteries of Nature** we have not solved. Hurricanes, for example, continue to occur and often cause massive devastation. Meteorologists cannot predict months in advance when and with what velocity a hurricane will strike a specific community. Polymorphism is a parallel phenomenon. We know that it will probably happen. But not why or when.

Unfortunately, there is nothing that we can do today to prevent a hurricane from striking any community or polymorphism from striking any drug."

Ritonavir

“... We [Abbott] tried everything: we conducted countless experiments. We reconditioned our facilities: We rebuilt facilities and new lines. We looked at alternative sites. We visited a number of other organizations around the World... to see if we could start clean in a new environment free of form II...”

“... In a matter of weeks – maybe five or six weeks, every place became contaminated with form II crystal...”

“... While we have speculated on the cause of this chemical transformation, we don't have conclusive proof what happened...”

THANK YOU !

Enable



Elettra Sincrotrone Trieste

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SCIENTIFICUPDATE

Evolve

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