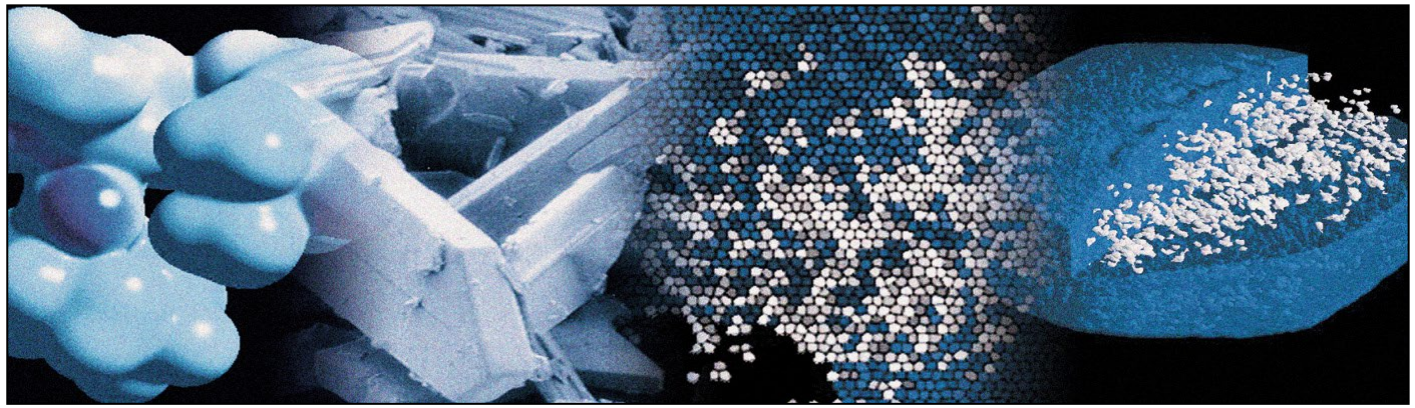
From Molecule to Materials to Medicine

A Celebration of 15 years of the Crystal Form Consortium (CFC) Accelerating the Development Journey Through the Application of Structural Sciences

Bob Docherty (West View House Consulting)
Elna Pidcock, Ghazala Sadiq, Andy Maloney (CCDC)

CCDC March 5th, 2024

Final Version



Overview of Presentation

Short Questions and Answers Interlude at End of Each Section

Background and Context – Why

- Historical Importance of Materials Sciences
- Recent examples showing continued relevancy in Industry
- Recent examples showing continued interest and excitement in industry and academia

A historical review of the landscape over 15 years

- The changing demands form Industry on Materials Sciences
- Risks, benefits, and challenges of acceleration for solid form selection timings
- Examples of progress and Decision trees around solid form options

Fusing Experimental and Digital Workflows – How

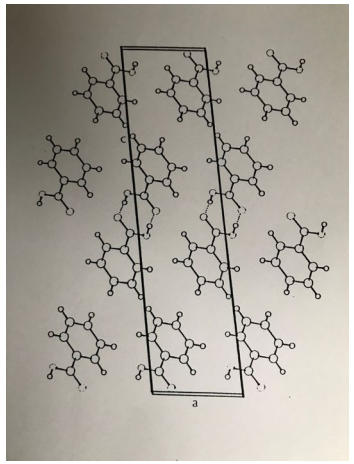
- Examples of Structural Science, Solid Form Tools and Computational Methods
- Particle Informatics Vignettes
- Critical role for the structural tools in underpinning product acceleration

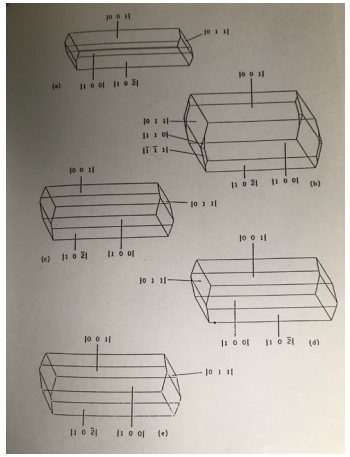
Future Outlook – Digital Design

- Re-shaping the Materials Sciences Knowledge Curve
- Digital Transformation, Digital Design and the Molecule to Medicine acceleration
- Crystallographic data as an integral digital thread through pharmaceutical development
- The CSD data trust opportunities partnering across Processing, Properties, Performance

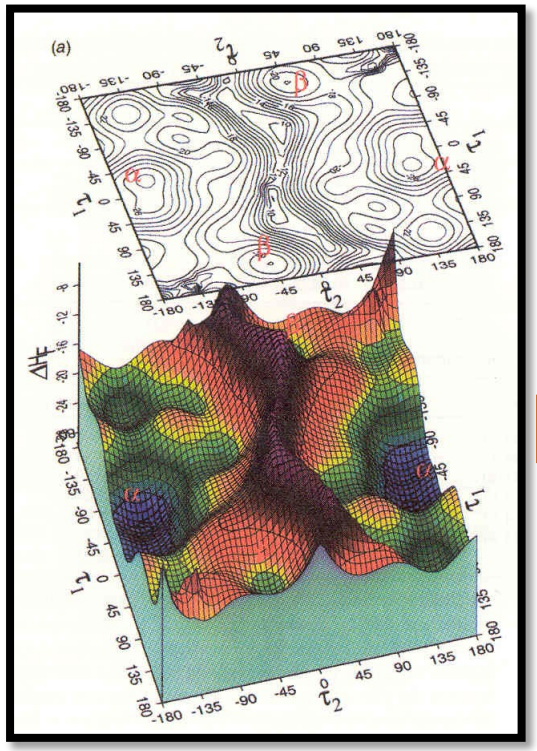
Journey to Being Here Today

CSD refcodes
Structure files





Conformational Polymorphs



o-acetamido-benzamide

Pfizer Institute for Pharmaceutical Materials Science

The Pfizer Institute for Pharmaceutical Materials Science

Pharmaceutical Materials Science's pivotal role

The integration of solid-form informatics into solid-form selection

N. Feeder, E. Pidcock, A. M. Reilly, G. Sadiq, C. L. Doherty, K. R. Back, P. Meenan, R. Docherty

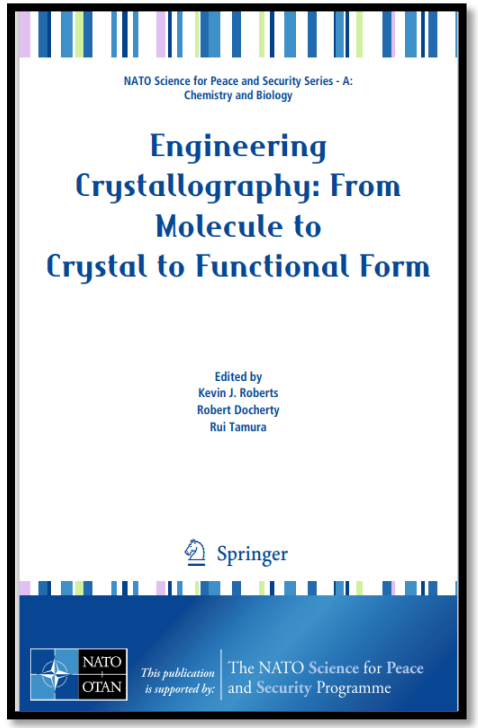
J Pharm Pharmacol. 2015, 67(6) : 857

Cross Industry

ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Cross Community

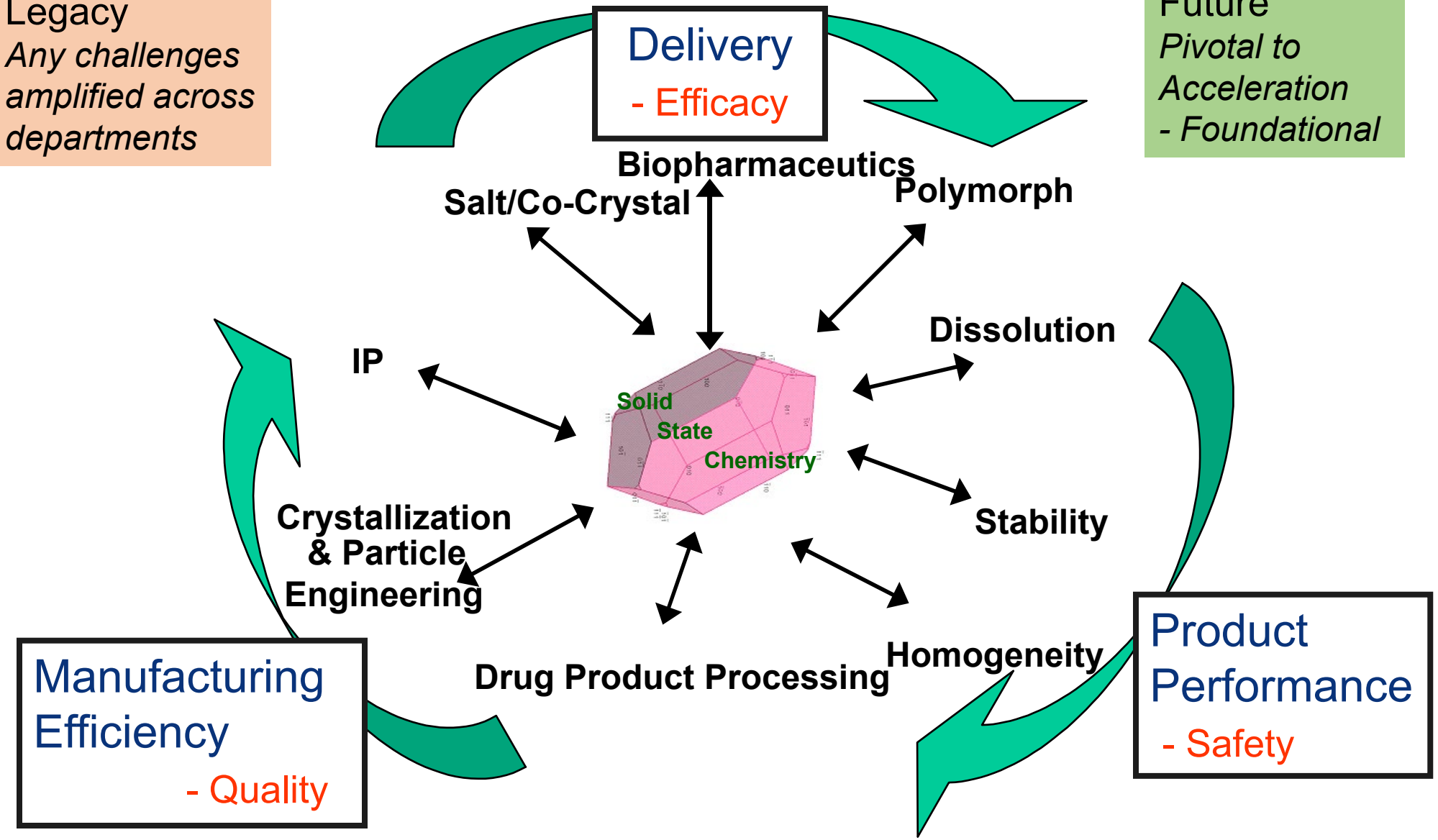


Reflections on this journey and Materials Sciences roles in Pfizer locally and globally helped shape the perspective and projections for this presentation

The Importance of Pharmaceutical Materials Science

Legacy
Any challenges amplified across departments

Future
Pivotal to Acceleration
- Foundational



Illustrations of the Industry Challenges Associated with Unexpected Solid Form Issues – Looking Back

Excellent overview of examples Allan Myerson *et al,* Annu. Rev. Chem. Biomol. Eng. 2011. 2:259–80

1998 Abbott Laboratories announced that it was experiencing manufacturing difficulties with the capsule formulation of the HIV protease inhibitor, Norvir (ritonavir).
Product withdrawal and reformulate to accommodate Form II.

Struggled to secure Form 1 in manufacturing facilities.
Reformulate new product

Schwarz Pharma recalled Neupro® (rotigotine transdermal system) at the end of April 2008. The decision to recall was due to the formation of rotigotine crystals in the patches.
Subsequent introduction of full cold chain manufacture and storage and reduction in shelf life of product to manage with the new form

Reduced shelf life and specific manufacturing conditions to control form in product

Is Effient the Tip of a Form Conversion Iceberg? (2009)
Lilly's participation in an FDA QbD pilot program uncovered an unusual issue. Late in the pivotal trials, analysis of the prasugrel drug substance found that the salt designed for commercial use back-converted to the less bioavailable free base.

Enhanced analytical control to achieve fixed ratio of free base and salt consistent with pivotal studies

Distillation of Recent Examples Showing Materials Sciences Still Pivotal to Product Realisation

Academic Perspective
Editorials: Crystal Growth & Design and Molecular Pharmaceutics (2021) and *'Sword of Damocles or Innovation Tools'* review (2022)

New Perspective on 'old challenges'
Form III of Ritonavir (2023)
CSP on Rotigotine (2019)

New polymorphs in WHO essential medicines
Dapsone Form V (2019)
Phenobarbital Form V

Solid Form Design still vital and highly relevant

ISPE : Accelerated Pharmaceutical Product Development Part 2

Registration, Commercialization CMC Lessons - Case Study 4 (2019)

Crystallography and Pandemic Response

Dexamethasone co-crystals (2022)
Remdesivir polymorphs (2021)

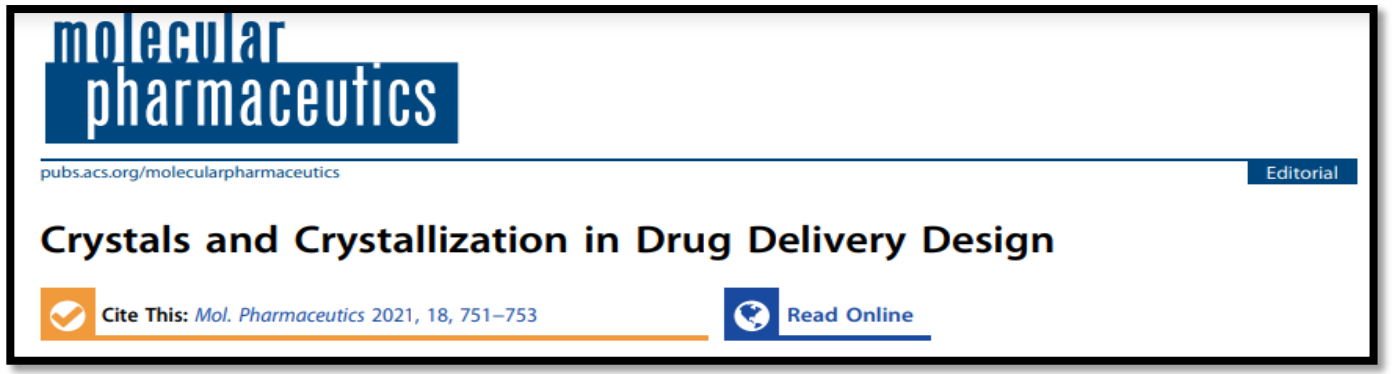
In the Top 20 best-selling small molecule drugs (2021)
Two products illustrating the balance of most stable form and lower bioavailability and metastable form and long-term stability control.

Form stability in drug product
BMS paper strategic risk management aligned to ICH Q6a
(2023)

New Products
Co-crystal of tramadol and celecoxib.
Solid form dictates performance profile
(2017 - 2021)

Additional references at the end of the slides/presentation

Academic Perspective
Building on Example From Previous Slide – Future Outlook


molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics Editorial

Crystals and Crystallization in Drug Delivery Design

Cite This: *Mol. Pharmaceutics* 2021, 18, 751−753 Read Online


CRYSTAL GROWTH & DESIGN

pubs.acs.org/crystal Editorial

Crystals and Crystallization in Drug Delivery Design

Cite This: *Cryst. Growth Des.* 2021, 21, 1375−1377 Read Online

ACCESS | Metrics & More | Article Recommendations


International Journal of *Molecular Sciences* MDPI

Review

The Relevance of Crystal Forms in the Pharmaceutical Field: Sword of Damocles or Innovation Tools?

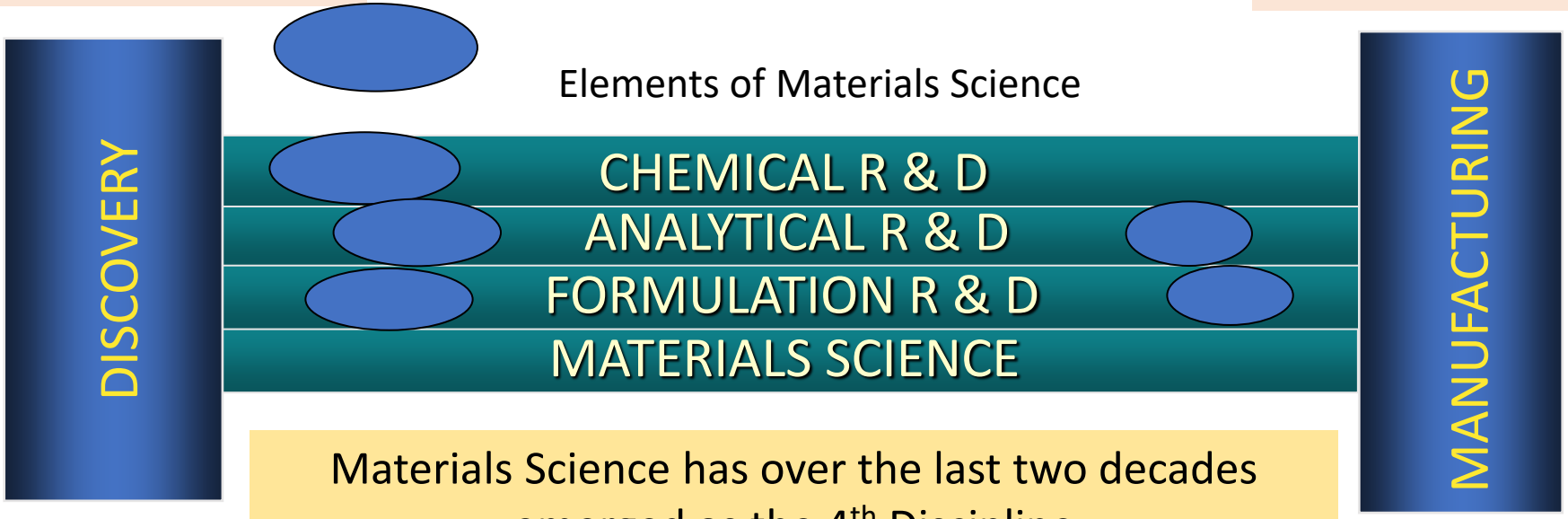
Dario Braga *, Lucia Casali and Fabrizia Grepioni

- Remains highly topical and challenging.
- Editorial perspectives reaching across different communities.
- Building on existing solid form activities and successes.
- Moving towards drug product with consideration for form in different product types
- Solid form integral to many aspects of drug delivery.
- Through engineering solid form attributes - deliver diversity of dosage forms that meet patients needs.
- *'Stressing why the quest for new crystal forms of any given API can still be both "joy and sorrow" for the academic and industrial researcher.'*

Materials Science - The 4th Discipline
Changing the Development Paradigm in Industry

INVENT THE MOLECULE

MAKE THE PRODUCT



Materials Science has over the last two decades emerged as the 4th Discipline

Continuing influence of academia with Materials Sciences at the heart of innovation

CMAC – Continuous Manufacturing and Advanced Crystallisation

SSPC - The Science Foundation Ireland Research Centre for Pharmaceuticals

CIMSEPP - Center for Integrated Material Science and Engineering of Pharmaceutical Products

Molecules, Materials, Medicines (M3): Linking Molecules to Medicines through Pharmaceutical Material Science Ö Almarsson and E. B. Vadas, Cryst. Growth Des. 2015, 15, 12, 5645–5647

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The Development Paradigm and Drug Product Design Challenges

Early Phases of Development (Speed)

- API synthetic route and process is still being developed
- Enabling dosage form being used
- Analytical methods are phase appropriate and not yet fully refined
- Solid form landscape being explored with *'enabling form'* to facilitate rapid clinical progress
- Long term chemical/physical stability being established

Materials Sciences - Confidence

Late Stages of Development (Robustness)

- API synthetic route locked, and drug product process established
- Commercially viable dosage form used
- Fully validated analytical methods including physical properties
- Commercial solid form landscape understood, and polymorph control (if needed) established
- Registration chemical/physical stability studies

12- 15 years

Discovery	Development	Manufacture
Select Molecule	*Design Product*	*Optimise Processes*

Tox PK/Safety Ph 2 Efficacy Phase III

Drug Development Process and Accelerated Strategy

Candidate Seeking to First Submission

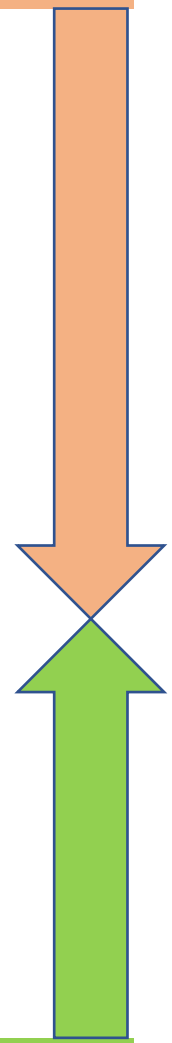
Traditional timelines – 12.25 years
Accelerated - 8.25 years
Super Accelerated - 5 years

ISPE Case Study on accelerated development and solid form summarised later illustrates challenge

Historical and Technological Evolution of Materials Science Over the Last Two Decades

Head of Materials Sciences perspective

- Delivering 'routine' characterisation of drug substance (DS) and drug product (DP) batches
- *State of the art* characterisation
- Small scale screening to aid optimum form selection
- High throughput systems to enhance legal protection of solid forms
- Structural perspective on solid form selection
- Small scale materials testing (compaction simulator)
- Surface characterisation techniques (e.g. AFM)
- *On-line* and *at-line* enhanced crystallisation and physical characterisation
- Solid Form Informatics and Crystal Structure Prediction at the heart of form selection
- Workflows to elaborate an API *target attribute profile* integrating crystal engineering and dosage form design at DS/DP interface
- Digitally enabled workflows at the heart of product realisation acceleration



Strategic Lead for Digital Design perspective

2008 to 2013

Tools emerging

Industrial challenges remain topical

Knowledge-based H-bond prediction to aid experimental polymorph screening
Peter T. A. Galek, Frank H. Allen, László Fábián and Neil Feeder
CrystEngComm, 2009,11, 2634-2639

Towards crystal structure prediction of complex organic compounds – a report on the fifth blind test
David A. Bardwell, Claire S. Adjiman, Yelena A. Arnautova, Ekaterina Bartashevich, *et al*
Volume 67 Part 6 December 2011 Pages 535-551

One in half a million: a solid form informatics study of a pharmaceutical crystal structure
Peter T. A. Galek, Elna Pidcock, Peter A. Wood, Ian J. Bruno and Colin R. Groom
CrystEngComm, 2012,14, 2391-2403

The industrial need and the academic opportunity emerge

Schwarz Pharma recalled Neupro® (rotigotine transdermal system) at the end of April 2008. The decision to recall was due to the formation of rotigotine crystals in the patches.

Is Effient the Tip of a Form Conversion Iceberg? (2009)
Lilly's participation in an FDA QbD pilot program uncovered an unusual issue. Late in the pivotal trials, analysis of the prasugrel drug substance found that the salt designed for commercial use back-converted to the less bioavailable free base.

Crystal Polymorphism in Chemical Process Development
A.Y. Lee, D. Erdemir, A.S. Myerson
Annual Review of Chemical and Biomolecular Engineering. Vol 2, 259-280 (2011)
Merck, BMS, MIT review

2014-2016

Tools and data into workflows

Challenges remain topical across community RSC, RPS, AAPS

Experimental and Structural Thread

Facts and fictions about polymorphism
Aurora J. Cruz-Cabeza, Susan M. Reutzel-Edens and Joel Bernstein
Chem. Soc. Rev., 2015,44, 8619-8635

Report on the sixth blind test of organic crystal structure prediction methods
Anthony M. Reilly, Richard I. Cooper, Claire S. Adjiman, Saswata Bhattacharya, et al
Volume 72 Part 4 August 2016 Pages 439-459

The Integration of Solid-Form Informatics into Solid-Form Selection Feeder, Neil; Pidcock, Elna; Reilly, Anthony M.; Sadiq, Ghazala; Doherty, Cheryl L.; Back, Kevin R.; Meenan, Paul; Docherty, Robert *Journal of Pharmacy and Pharmacology 67(6), 857-868. (2015)*

Pharmaceutical Properties—the Importance of Solid Form Selection
Robert Docherty and Nicola Clear *The Handbook of Medicinal Chemistry : Principles and Practice (Editors Andrew Davis, Simon E Ward) The Royal Society of Chemistry, Cambridge (2014).*

Low Solubility in Drug Development: De-convoluting the Relative Importance of Solvation and Crystal Packing Docherty, Robert; Pencheva, Klimentina; Abramov, Yuriy A. *Journal of Pharmacy and Pharmacology 67(6), 847-856 (2015)*

Solid form changes during drug development: good, bad, and ugly case studies
Ann Newman & Robert Wenslow
AAPS Open volume 2, Article number: 2 (2016)

2017-2019

CCDC at the heart of the community

Tools into the workflows

A Million Crystal Structures: The Whole Is Greater than the Sum of Its Parts
Robin Taylor and Peter A. Wood*
Chem. Rev. 2019, 119, 16, 9427–9477

The CSD Drug Subset: The changing chemistry and crystallography of small molecule pharmaceuticals'
M. Bryant, S. Black, H. Blade R. Docherty, A. Maloney, S. Taylor,
J. Pharm. Sciences (2019), 108(5), 1655-1662.

Particle Informatics: Advancing our Understanding of Particle Properties Through Digital Design Bryant, Mathew J.; Rosbottom, Ian; Bruno, Ian J.; Docherty, Robert; Edge, Colin M.; Hammond, Robert B.; Peeling, Robert; Pickering, Jonathan; Roberts, Kevin J.; Maloney, Andrew G. P.
Crystal Growth & Design (2019), 19(9), 5258-5266.

A vision realized, the importance of a data trust

Impact of Crystal Structure and Molecular Conformation on the Hydration Kinetics of Fluconazole Basford, Patricia A, Back, Kevin R, Cram, Michael, Docherty Robert, Davey, Roger J, Cruz-Cabeza, Aurora J.
Crystal Growth & Design (2019), 19(12), 7193-7205

Use of Crystal Structure Informatics for Defining the Conformational Space Needed for Predicting Crystal Structures of Pharmaceutical Molecules.
Price, SL; Iuzzolino, L; Reilly, AM; McCabe, P;
Journal of Chemical Theory and Computation , 13 (10) pp. 5163-5171 (2017)

Regulatory Classification of Pharmaceutical Co-Crystals Center for Drug Evaluation and Research (CDER) Pharmaceutical Quality/CMC February 2018
(see previously for Initial Guidance 2013, and Revised Guidance 2016)

2020-2023

Still highly relevant for pharmaceutical product design

Industrial application and outcomes

From structure to crystallization and pharmaceutical manufacturing: the CSD in CMAC workflows
Lauren E. Hatcher, Ayrton J. Burgess Pollyanna Payne and Chick C. Wilson
CrystEngComm, 2020, 22, 7475-7489

Crystals and Crystallization in Drug Delivery Design
Lynne S. Taylor, Doris E. Braun, and Jonathan W. Steed
Cryst. Growth Des. 2021, 21, 3, 1375–1377

Aromatic Interactions in the Cambridge Structural Database: Comparison of Interaction Geometries and Investigation of Molecular Descriptors as an Indicator of Strong Interactions
Elna Pidcock, Ghazala Sadiq, Joanna S. Stevens Robert D. Willacy
Cryst. Growth Des. 2022, 22, 1, 788–802

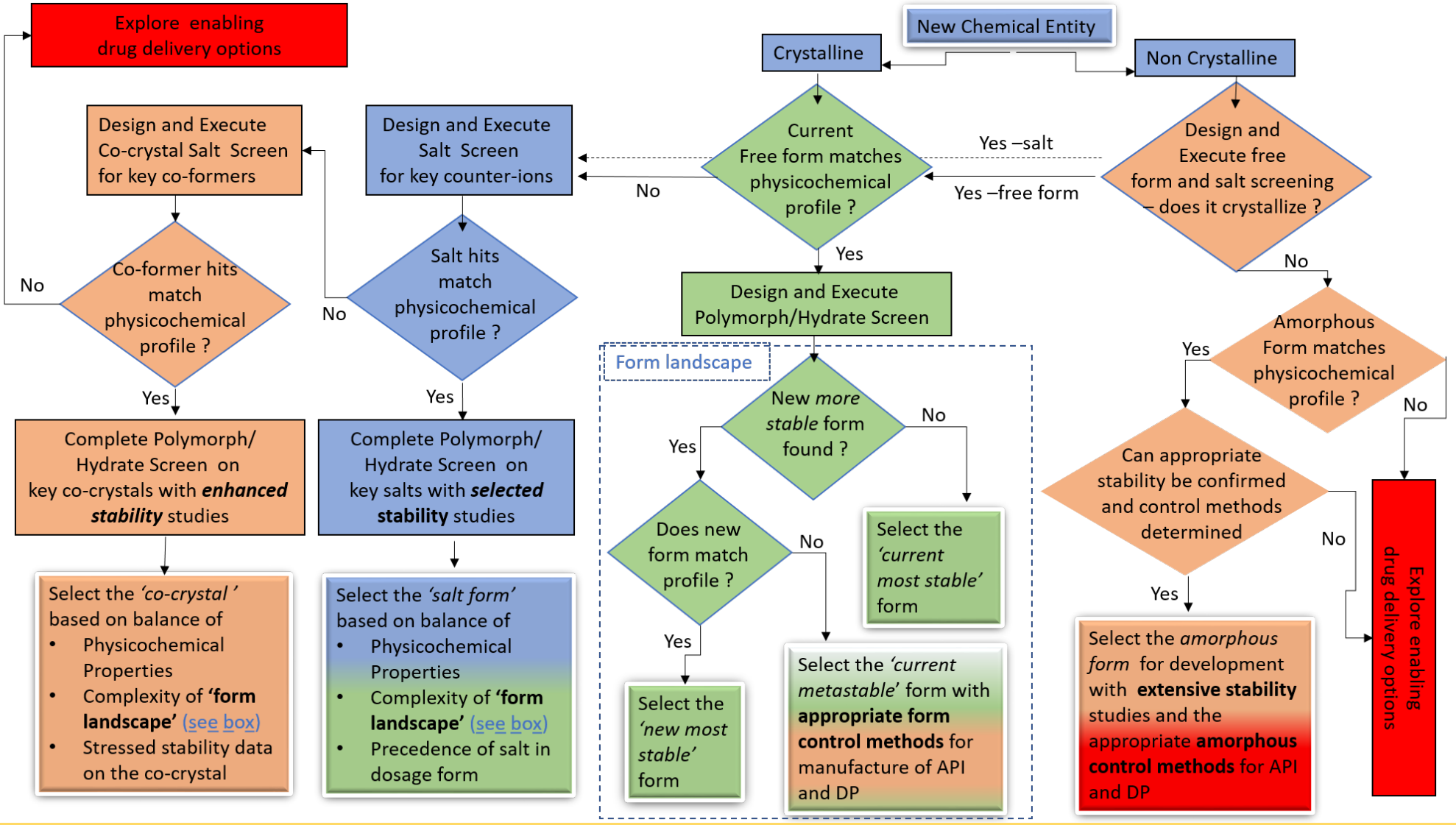
Remains highly topical – Properties, Processing , Performance

First global analysis of the GSK database of small molecule crystal structures
Leen N. Kalash, Jason C. Cole Royston C. B. Copley Colin M. Edge, Alexandru A. Moldovan Ghazala Sadiq and Cheryl L. Doherty
CrystEngComm, 2021, 23, 5430-5442

Co-crystal of Tramadol Hydrochloride–Celecoxib (ctc): A Novel API–API Co-crystal for the Treatment of Pain October 2021
ESTEVE ANNOUNCES FDA APPROVAL OF A NOVEL CO-CRYSTAL FORM OF CELECOXIB AND TRAMADOL FOR THE MANAGEMENT OF ACUTE PAIN

Strategies for Managing Solid Form Transformation Risk in Drug Product.
U. Kestur, A. Patel et al
J. Pharm. Sciences (2023) 112, 4, 909
BMS paper fusing stability case studies to ICHQ6a

Solid Form Selection Decision Tree (2023)



Pharmaceutical Properties—the Importance of Solid Form Selection Cheryl Doherty, Amy Robertson, Robert Docherty and Nicola Clear. Chapter 22, The Handbook of Medicinal Chemistry. Principles and Practice (Editors Andrew Davis, Simon E Ward) The Royal Society of Chemistry, Cambridge (2023). Figure 22.7

Solid Form Approvals - A Preliminary* Perspective

Three data streams looked at
(1) The FDA approvals for NDA in 2015 and (2) The FDA approvals for NDA in 2023-
(3) The Top25 best selling small molecule drugs in 2021 – reviewed in more depth
Work in progress still connecting these with broader reviews

- Based on description on FDA website and review of approved NDA label (some variation and interpretation that need to be clarified)

- Three and four **combination products** in 2015 and 2023 respectively
- **First in class** remains the same at 36 %
- Increase in **Fast Track Programs** from 31% to 45%

- Similar number of small molecules approved
  - 32 in 2015
  - 34 in 2023
- General increase in biologics over last 15 years
- It is worth noting that between 2010 and 2020 over 75% of approvals were small molecules

Dean G. Brown* and Heike J. Wobst*
J. Med. Chem. 2021, 64, 5, 2312–2338

Top 25 small molecule best selling drugs have sales of around $125bn

• Cardiovascular	3
• Oncology	7
• Infectious Diseases	4
• Diabetes	3
• Neurology	3

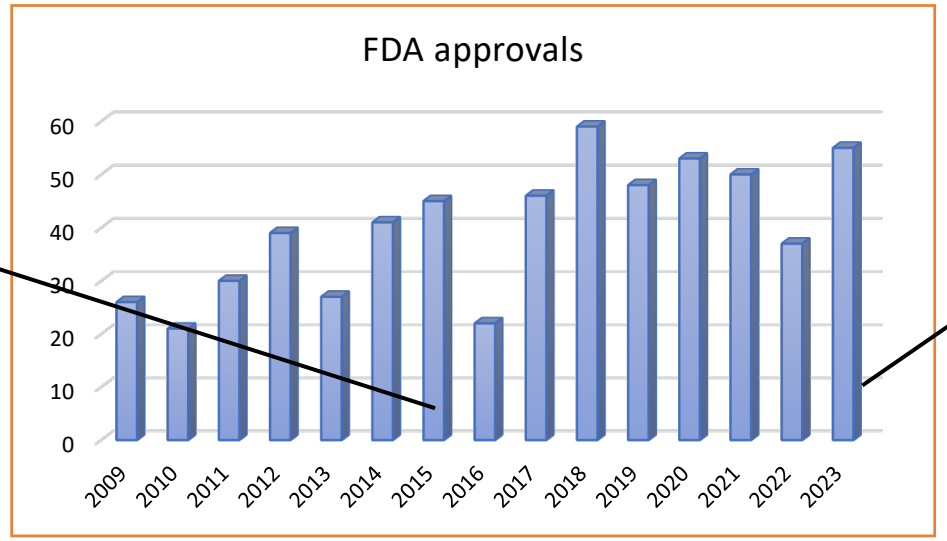
M. H. Qureshi, R. Williams, and C. Marshall from the Njarðarson Group (The University of Arizona

An initial review of FDA approvals in 2015 and 2023

Dosage Forms 2015

IR tablet	45%
IR capsule	27%
Injections	18%
Powder (IV)	3%
Oral suspension	3%
Oral granules	3%

One instance of single API with two dosage forms



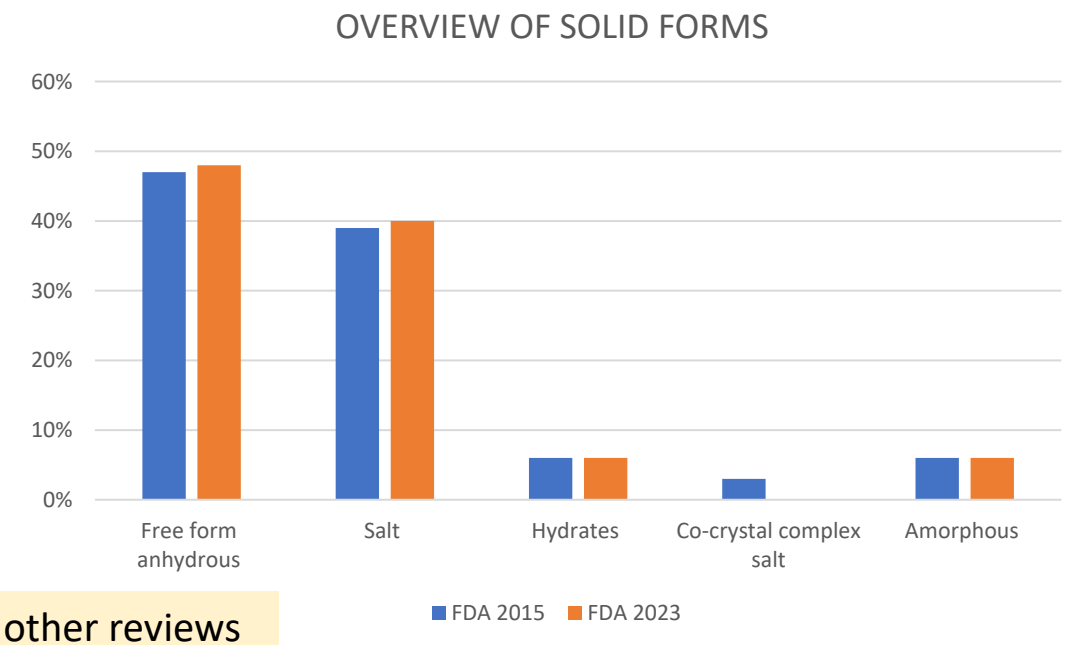
Dosage Forms 2023

IR tablet	45%
IR capsules	23%
Injections	13%
Ophthalmic solutions	6%
Oral susp./solution	6%
Topical Gel	3%
Nasal spray	3%

The topical gel contains 4 related API structures

Reviews suggest dosage forms dominated by oral dosage forms at 62% with injections next at 22%

Pharmaceutics 2018, 10, 263



Overall, **43%** of all pharmaceutical products are salts. Specifically for 2015 to 2019 that number is slightly higher at **48%**

Drug Discovery Today, Volume 26, Issue 2, 2021, 384-398,

Work in progress fusing this to other reviews

An initial* review of the crystal chemistry of the Top 25 best selling drugs (2021)

Rather than an individual year, profile the bestselling drug molecules developed over the timeframe

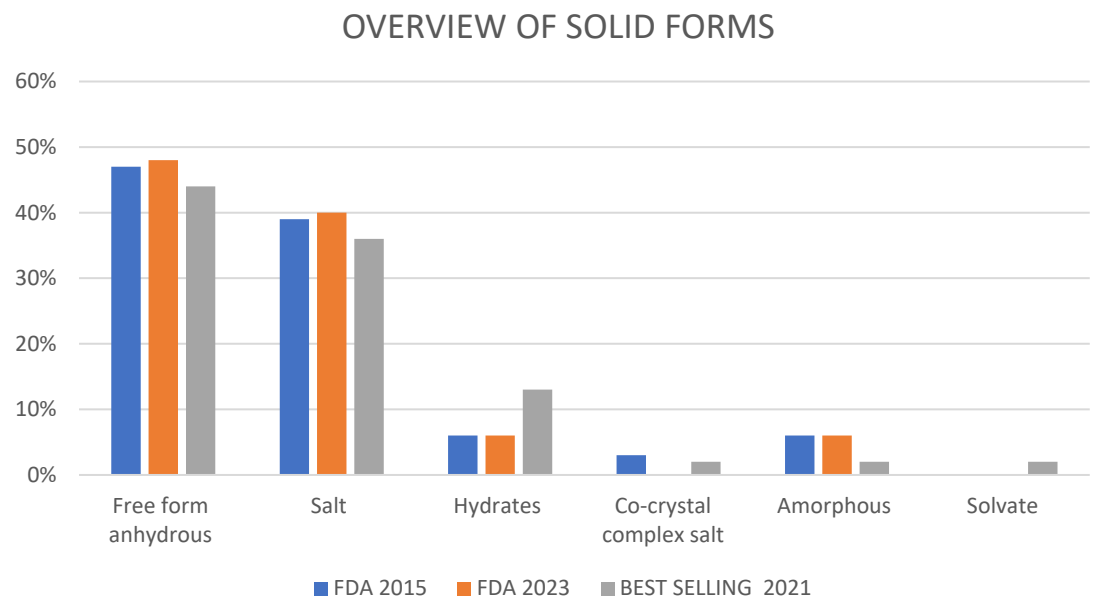
Solid Forms

- Free form anhydrous* 44%
- Salt 36%
- Hydrate ** 13%
- Co-crystal complex salt 2%
- Amorphous 2%
- Solvate 2%

** Two of these converted to spray dried dispersion (SDD) for one product.*

***Four salts are also are hydrates*

More than 25 entries due to five combination products



Dosage Forms

- IR tablet 50%
- IR capsules (one CR) 25%
- IR capsule (liquid) 12%
- Liquid/POS for infusion 8%
- Suspension for injection 4%

CSD REFCODES

- REFCODES linked in the CSD - 26 (84%)
- 12 of these appear to be the commercial form *
- No REFCODES in the CSD - 5**
- * Preliminary results - still work still in progress
- ** Two of these have PXRD structures reported

***Work in progress fusing this to other reviews**

Anhydrous and salt forms in tablets and capsules remain an important engine room to deliver medicines

ISPE : Accelerated Pharmaceutical Product Development
Part 2 Case Study 4 - Features September October 2019

Background

- Case study 4 involved a small molecule NDA submission after phase 2 clinical data.
- Submission after phase 2 clinical data was potentially 6 years shorter than "typical".

Super-Accelerated

The specific solid form challenge was:

- The solid-state of the drug substance form needed to be changed after phase 1 studies.

Additional background challenges were:

- The early drug substance synthetic route was not amenable to the scale of manufacture
- Phase 2 tablet clinical formulation was an enabled tablet suitable for rapid entry to clinic, but not commercial 'ready'.

Major activities carried out the project team were:

- A broad screen of solid-state forms was performed, supported by predictive tools and tablet-ability studies.
- A relative bioavailability (BA) study was conducted between the original phase 1 form and the new proposed commercial form.
- Once relative BA was shown, phase 2 pivotal clinical studies were started using the new proposed commercial form.

Additional risks identified by sponsor

If another, more suitable (e.g., more stable), form were to be found later in development, may need to redo the ICH stability studies and conduct a BE study. These additional studies would have involved significant delay and increased costs.

Outcomes

Switching quickly and early from the enabling form to the intended commercial form allowed for early commitment of the preferred drug substance form to clinical supplies for pivotal studies and to inclusion in the commercial tablet/ICH stability program.

Accelerated Pharma Product Development, Registration, Commercialization, & Life Cycle CMC Lessons Part 1 | Pharmaceutical Engineering (ispe.org)

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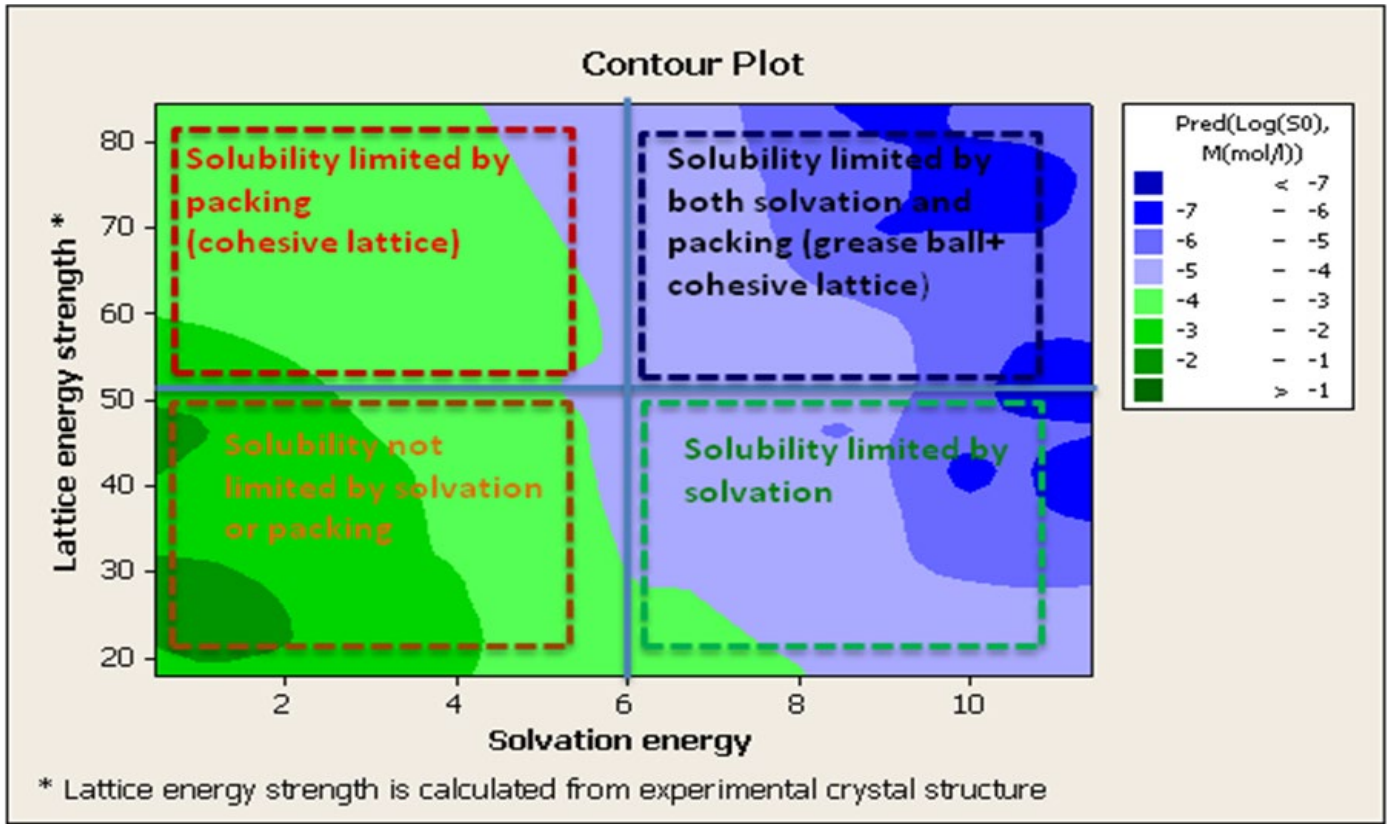
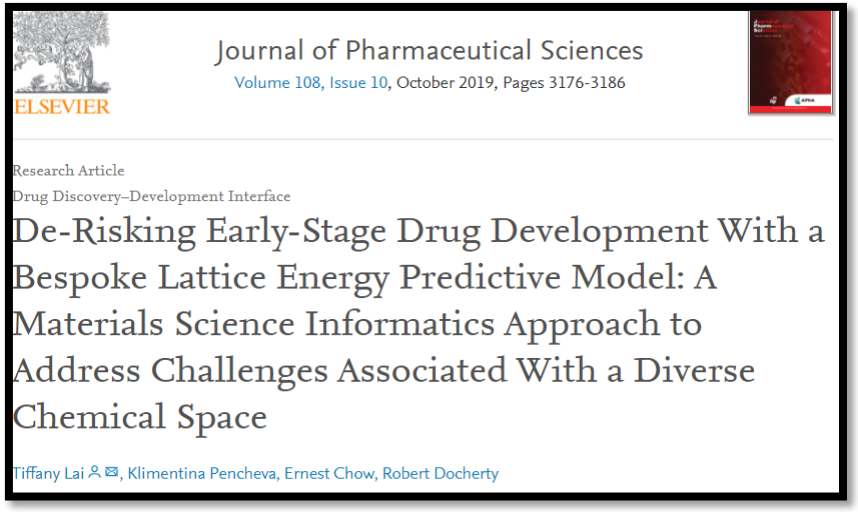
Discovery: Properties - Solvation-Packing Grid



- Add more compounds, especially in packing limited solubility quadrant
- Use pairs of polymorphs to explore vertical part of surface
- Use matched molecular pairs to hop across different parts of surface
- Develop a fast and accurate lattice energy estimation tool

Discovery: Properties – Lattice Energy Estimation



ELSEVIER

Journal of Pharmaceutical Sciences

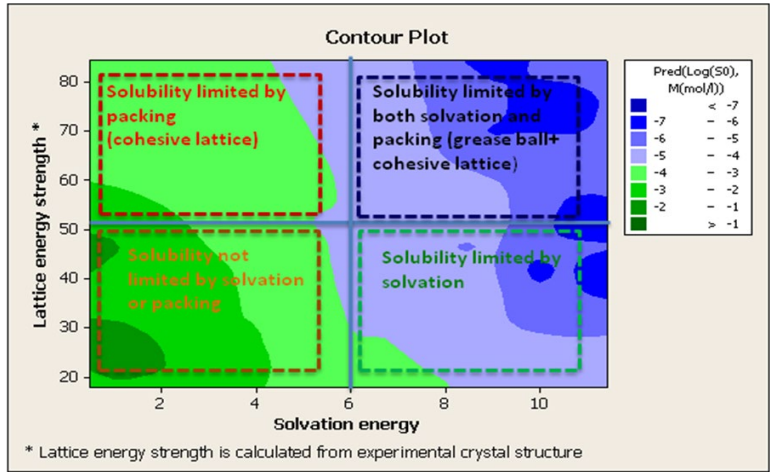
Volume 108, Issue 10, October 2019, Pages 3176-3186

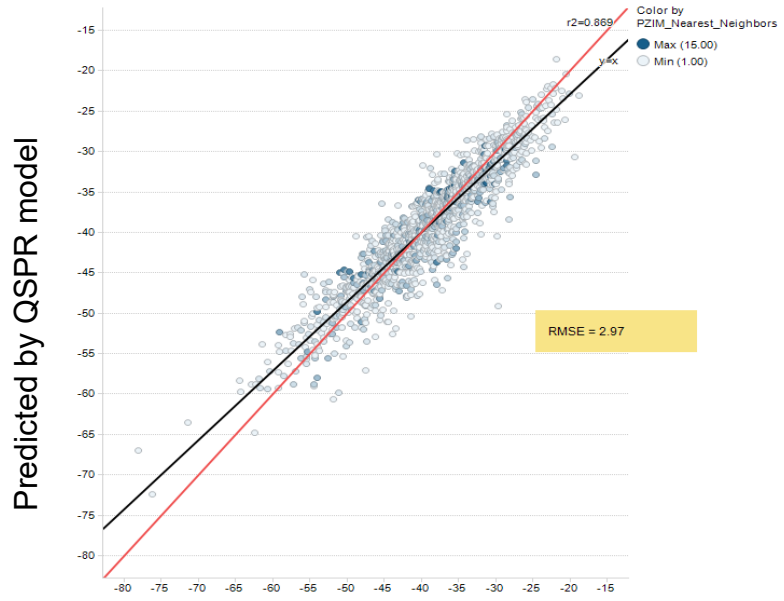
Research Article

Drug Discovery–Development Interface

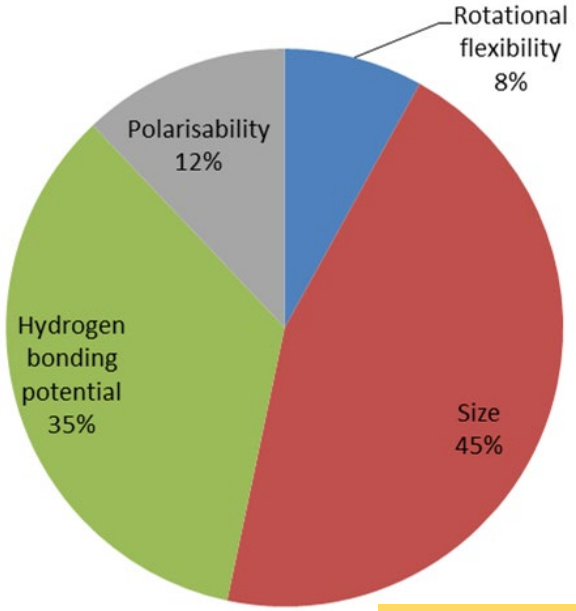
De-Risking Early-Stage Drug Development With a Bespoke Lattice Energy Predictive Model: A Materials Science Informatics Approach to Address Challenges Associated With a Diverse Chemical Space

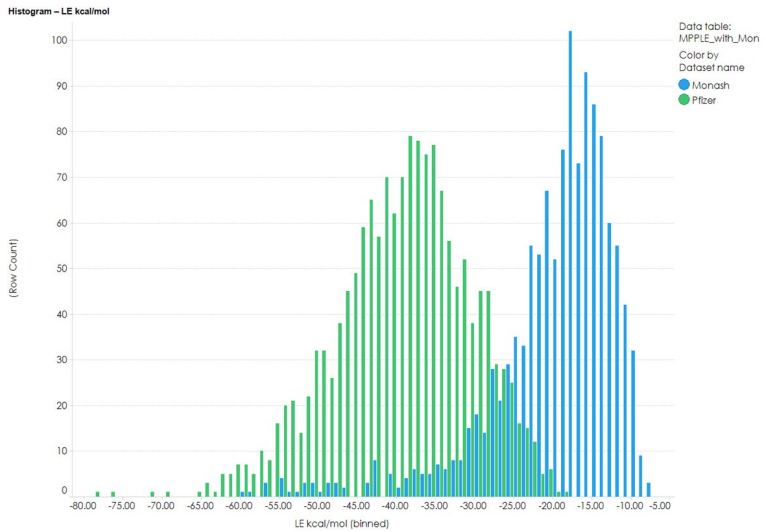
Tiffany Lai, Klimentina Pencheva, Ernest Chow, Robert Docherty





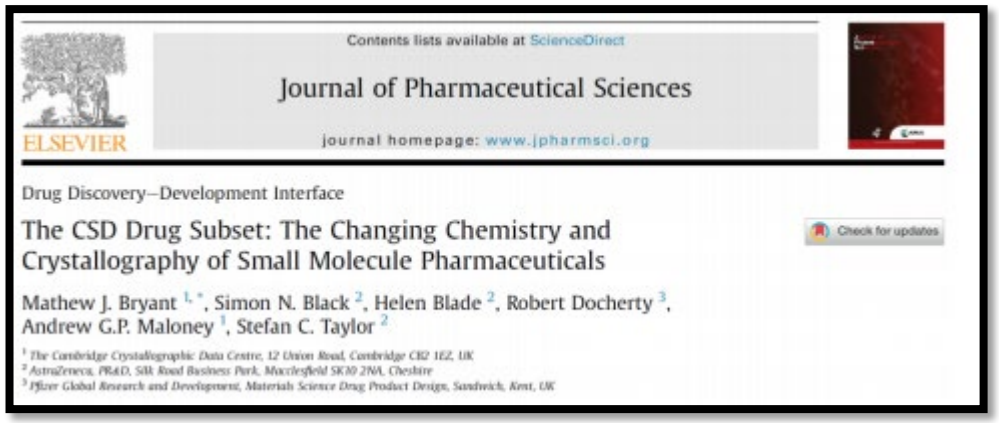
Calculated from crystal structure





Data set and model exploration and comparisons

Structural Science -The Power of a ‘Data Trust’



Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

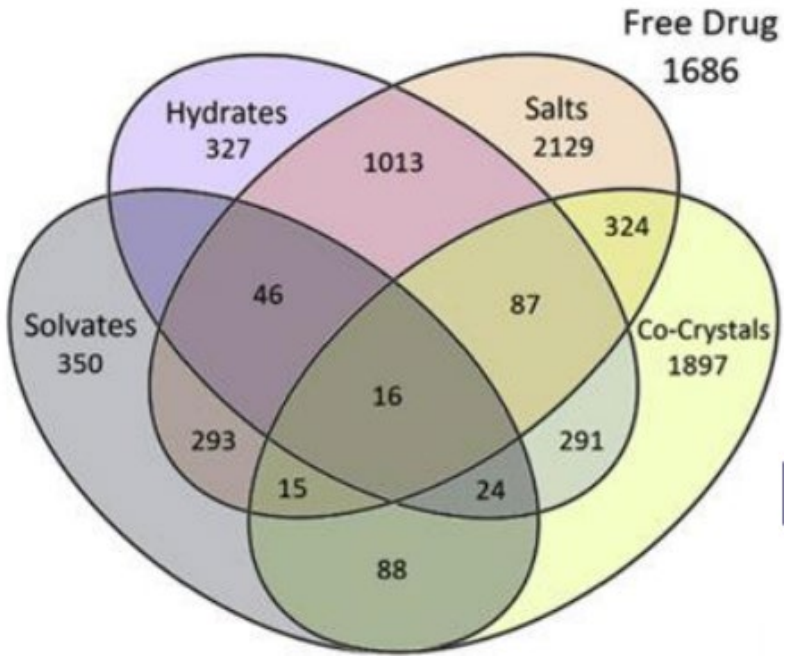
Drug Discovery–Development Interface

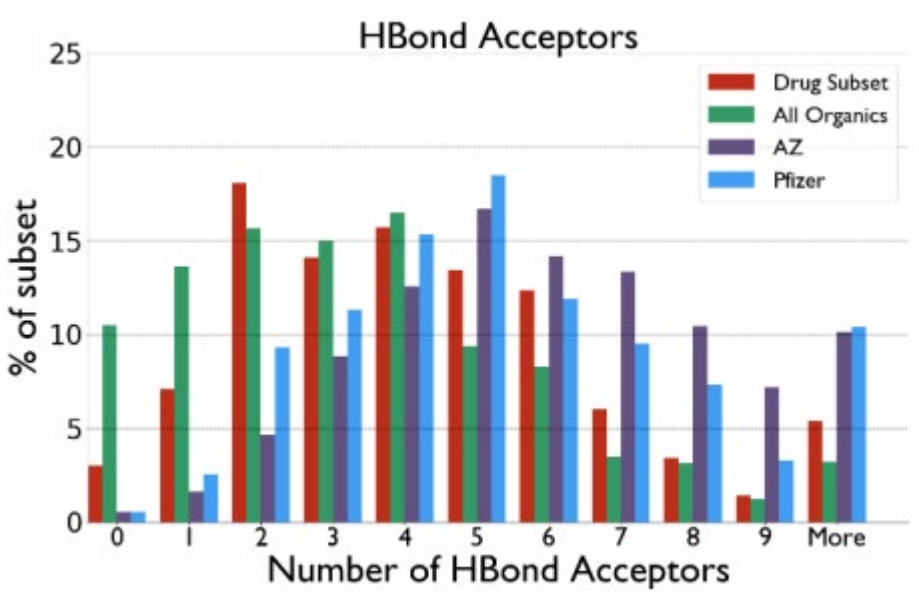
The CSD Drug Subset: The Changing Chemistry and Crystallography of Small Molecule Pharmaceuticals

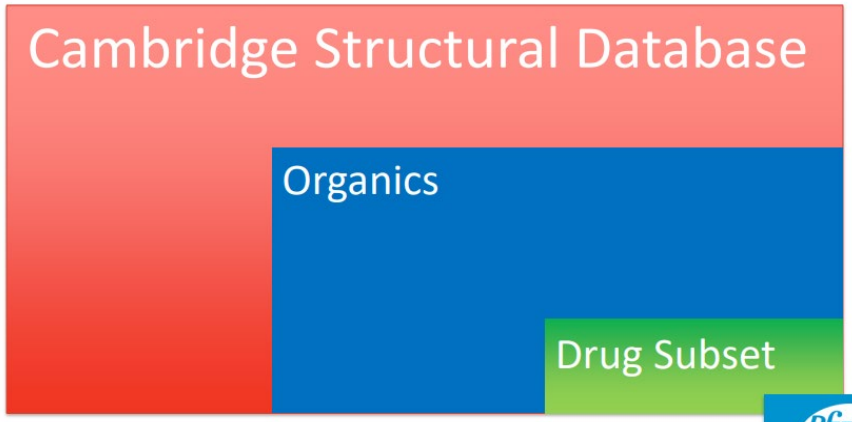
Check for updates

Mathew J. Bryant [1,*], Simon N. Black [2], Helen Blade [2], Robert Docherty [3], Andrew G.P. Maloney [1], Stefan C. Taylor [2]

[1] The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK
[2] AstraZeneca, PR&D, Silk Road Business Park, Macclesfield SK10 2NA, Cheshire
[3] Pfizer Global Research and Development, Materials Science Drug Product Design, Sandwich, Kent, UK







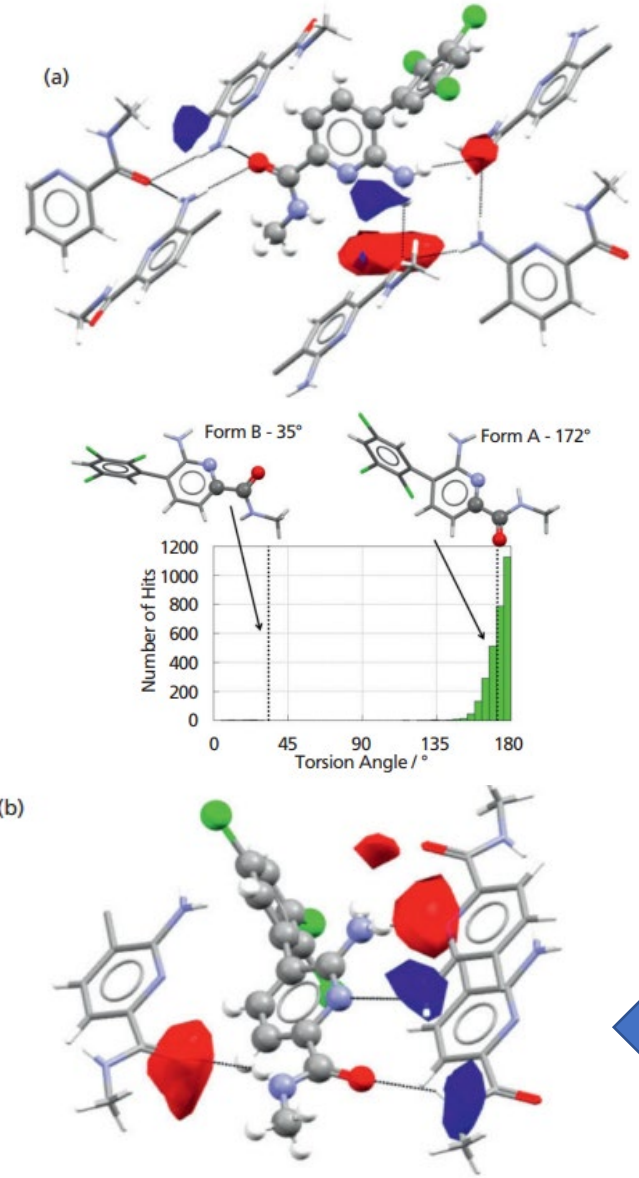
CCDC acting as a data trust model exploration & validation

Kevin Back, IUPAC, Paris 2019

Pfizer Database

Other companies’ databases

Solid Form Informatics and Fusion with Crystal Structure Prediction



Form A - first form found in early screening

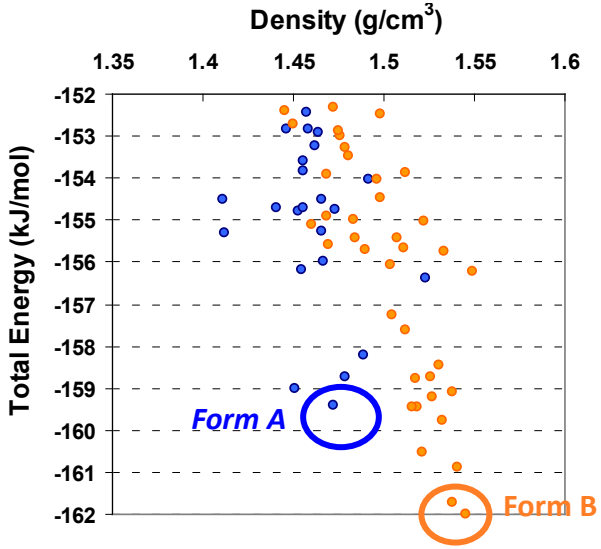
Solid Form informatics suggests not an optimal match of hydrogen bond donors and acceptors.

Crystal Structure Prediction showed Form A as the best packing for given *'closed conformation'* But a more *'open conformation'* packs better

Computational methods used to determine solvents that prefer '*open conformation*'

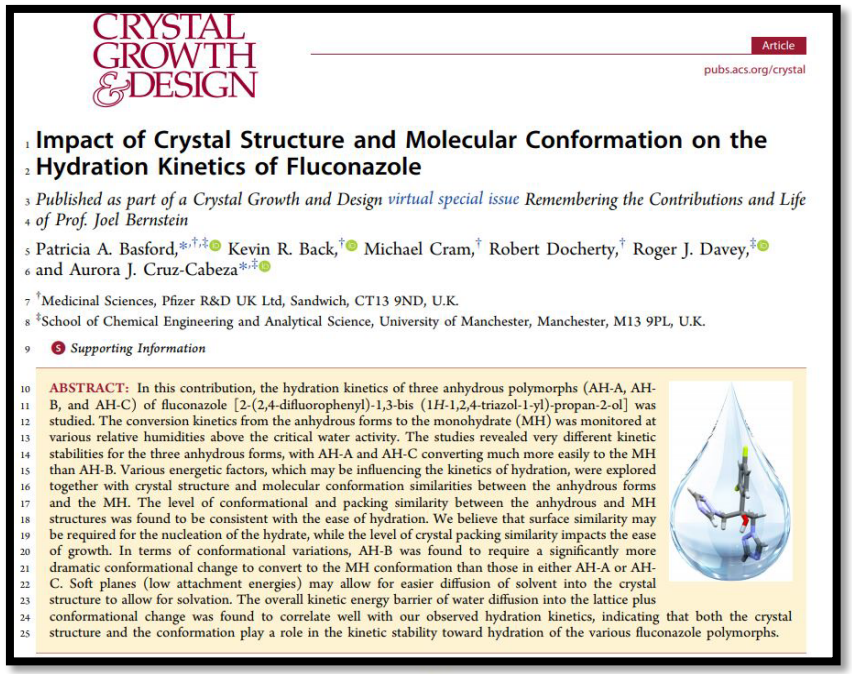
Targeted crystallisation studies in these solvents find Form B a new more stable anhydrous form

The Integration of Solid-Form Informatics into Solid-Form Selection. Feeder, N; Pidcock, E; Reilly, A. M.; Sadiq, G; Doherty, C. L.; Back, K. R.; Meenan, P; Docherty, R. *Journal of Pharmacy and Pharmacology 67(6), 857 (2015)*



C. Doherty, N.Feeder, K Pencheva and T. Mano, Chapter 5.1 "Control and Assessment of Polymorphism in Pharmaceutical Development", 2011, KK IMC Book, Tokyo, Japan.

Stability - Digital Design Enabled Workflows



CRYSTAL GROWTH & DESIGN

Article

pubs.acs.org/crystal

Impact of Crystal Structure and Molecular Conformation on the Hydration Kinetics of Fluconazole

Published as part of a Crystal Growth and Design virtual special issue Remembering the Contributions and Life of Prof. Joel Bernstein

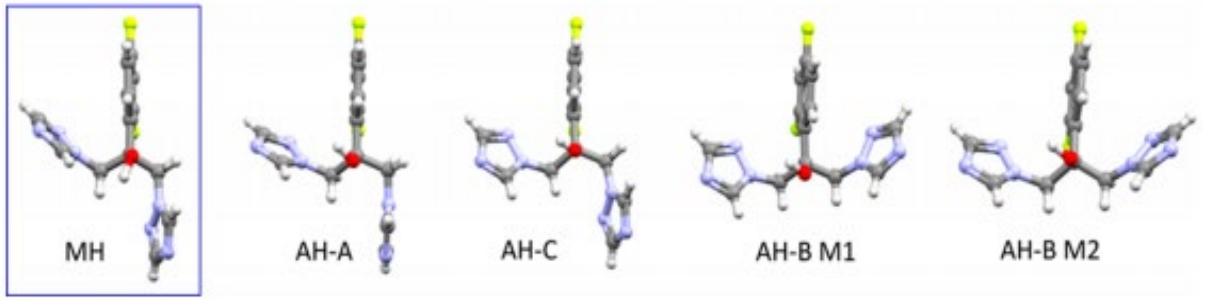
Patricia A. Basford,[*,†,‡] Kevin R. Back,[†] Michael Cram,[†] Robert Docherty,[†] Roger J. Davey,[‡] and Aurora J. Cruz-Cabeza[*,‡]

[†]Medicinal Sciences, Pfizer R&D UK Ltd, Sandwich, CT13 9ND, U.K.

[‡]School of Chemical Engineering and Analytical Science, University of Manchester, Manchester, M13 9PL, U.K.

Supporting Information

ABSTRACT: In this contribution, the hydration kinetics of three anhydrous polymorphs (AH-A, AH-B, and AH-C) of fluconazole [2-(2,4-difluorophenyl)-1,3-bis (1*H*-1,2,4-triazol-1-yl)-propan-2-ol] was studied. The conversion kinetics from the anhydrous forms to the monohydrate (MH) was monitored at various relative humidities above the critical water activity. The studies revealed very different kinetic stabilities for the three anhydrous forms, with AH-A and AH-C converting much more easily to the MH than AH-B. Various energetic factors, which may be influencing the kinetics of hydration, were explored together with crystal structure and molecular conformation similarities between the anhydrous forms and the MH. The level of conformational and packing similarity between the anhydrous and MH structures was found to be consistent with the ease of hydration. We believe that surface similarity may be required for the nucleation of the hydrate, while the level of crystal packing similarity impacts the ease of growth. In terms of conformational variations, AH-B was found to require a significantly more dramatic conformational change to convert to the MH conformation than those in either AH-A or AH-C. Soft planes (low attachment energies) may allow for easier diffusion of solvent into the crystal structure to allow for solvation. The overall kinetic energy barrier of water diffusion into the lattice plus conformational change was found to correlate well with our observed hydration kinetics, indicating that both the crystal structure and the conformation play a role in the kinetic stability toward hydration of the various fluconazole polymorphs.



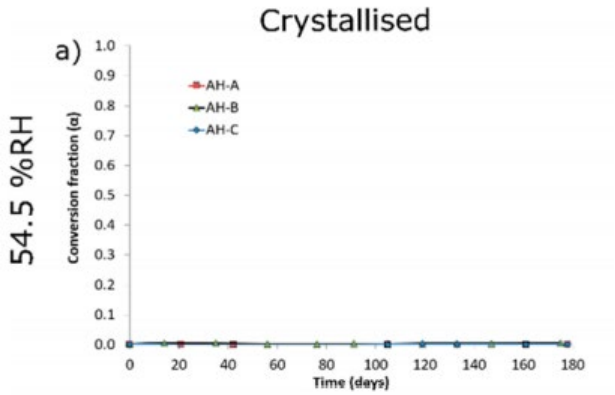
Classical Materials Sciences

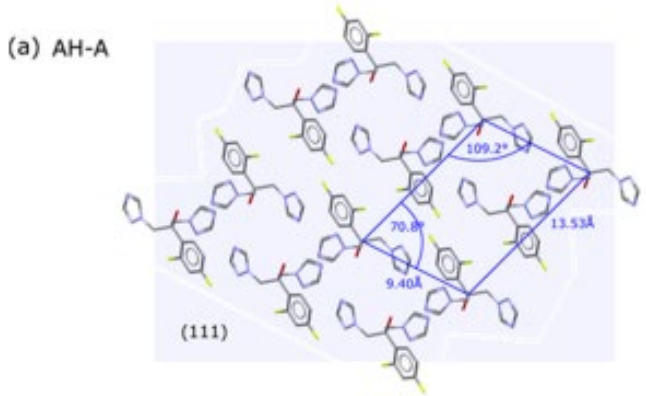
PXRD, DSC, DVS, SEM

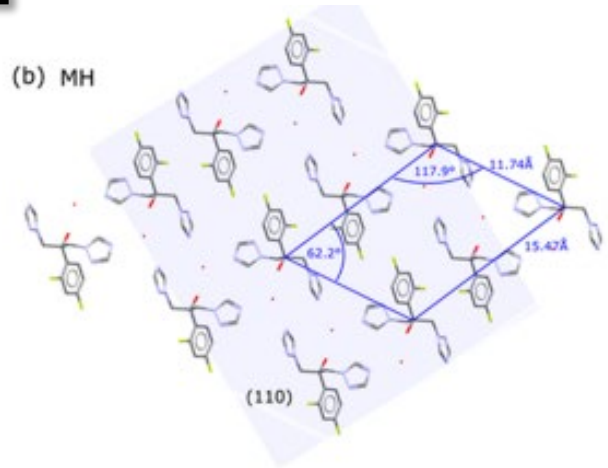
Critical water activity

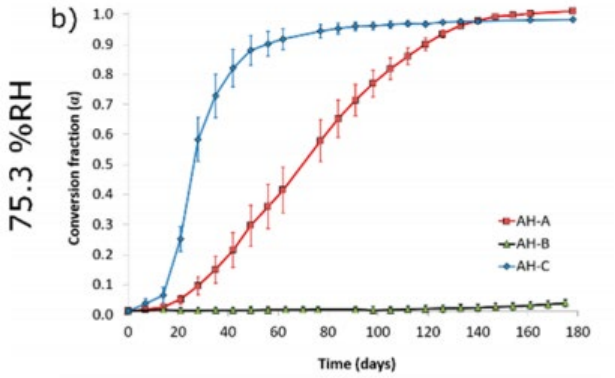
Elegant stability studies

Milled and seeded materials

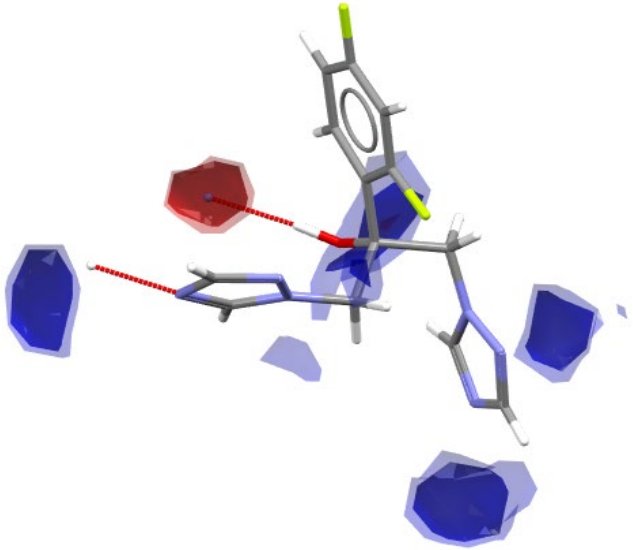




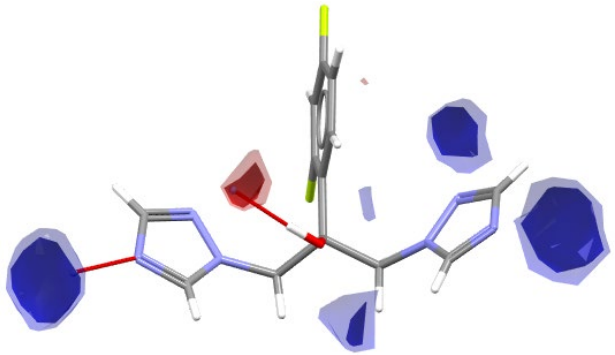




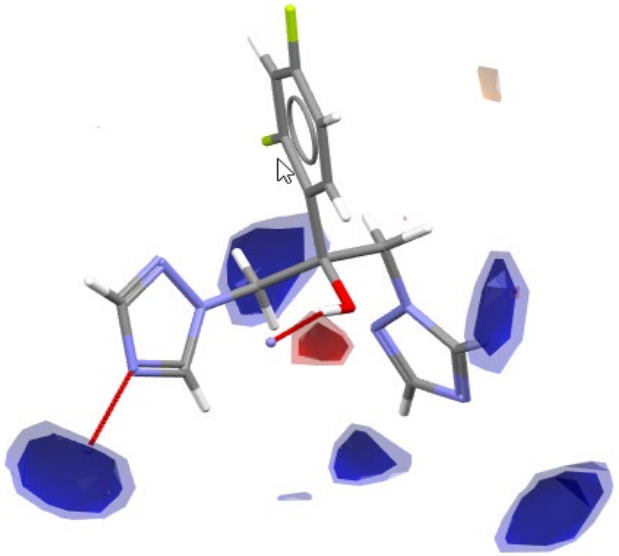
Stability - Fusion of Experimental and Structural Data



Form A



Form B



Form C

Jo Stevens unpublished work

Integrated across electronic supporting information from paper cited previous slide and from supporting information on *Conformational Change Initiates Dehydration in Fluconazole Monohydrate*
P. A. Basford*, C A. Cameron, and A J. Cruz-Cabeza
Cryst. Growth Des. 2020, 20, 9, 6044–6056

Form	1. DSC	2. Heat of solution	3. Lattice energy
Form B	-3.6	-3.0	-3.5
Form A	-2.4	-1.9	-1.7
Form C	0	0	0

Digital Definition of a Crystal – Norvir revisited
One of 2023 Outstanding Manuscript Awards by the AAPS

The 20th anniversary of the seminal paper by Bauer *et al*

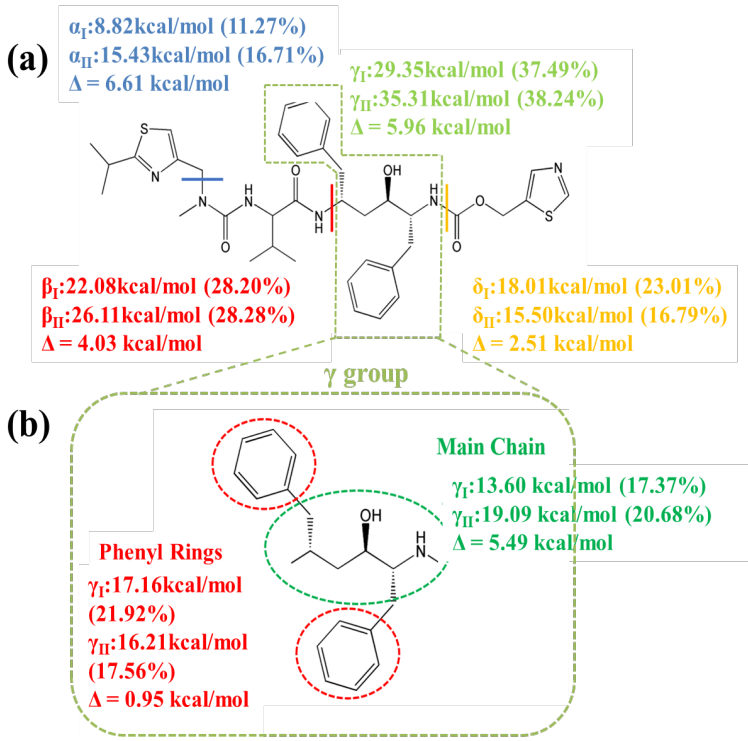
Ritonavir: An Extraordinary Example of Conformational Polymorphism. Pharm Res. 2001;18(6):859-66.

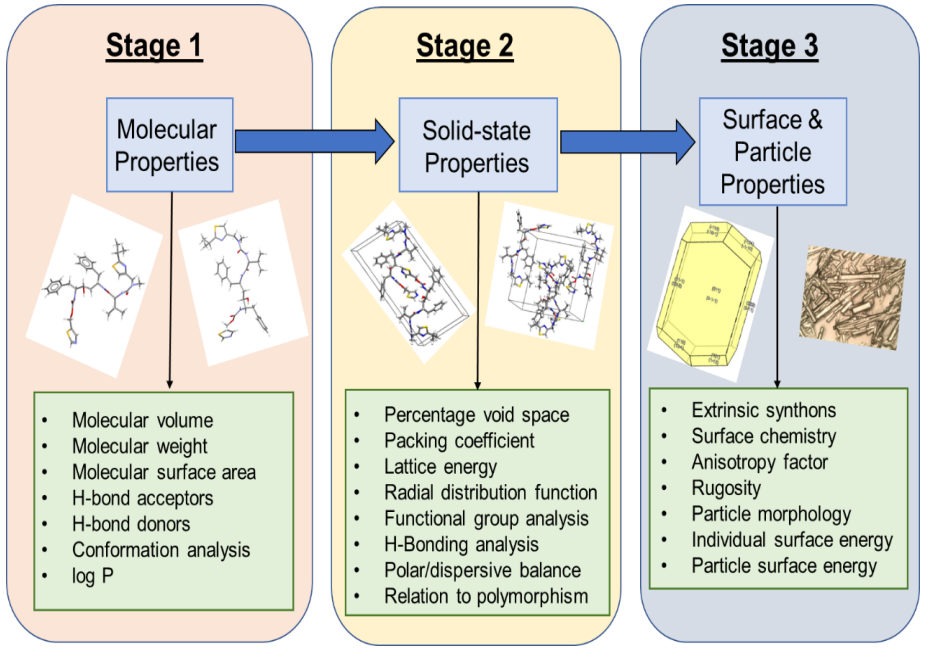
Pharm Res (2021) 38:971–990
https://doi.org/10.1007/s11095-021-03048-2

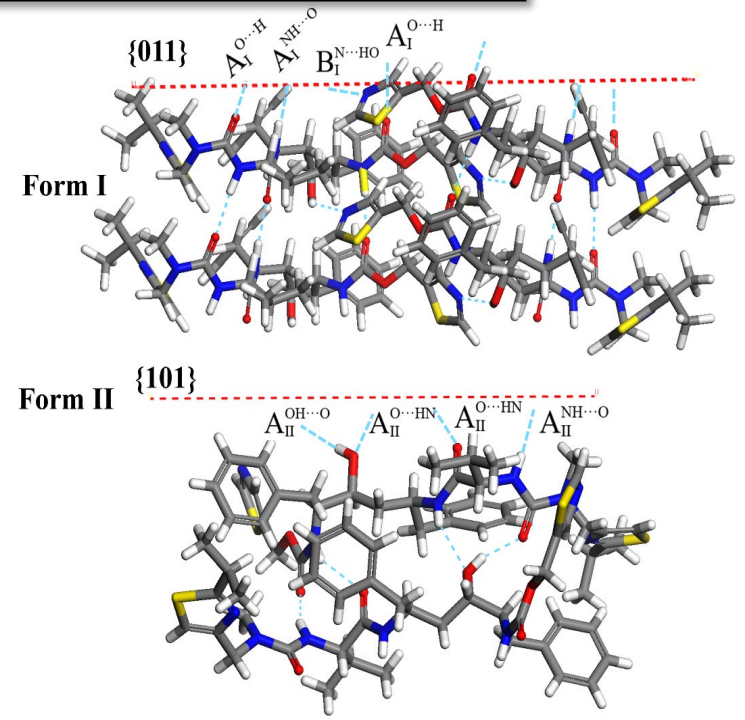
RESEARCH PAPER

Molecular, Solid-State and Surface Structures of the Conformational Polymorphic Forms of Ritonavir in Relation to their Physicochemical Properties

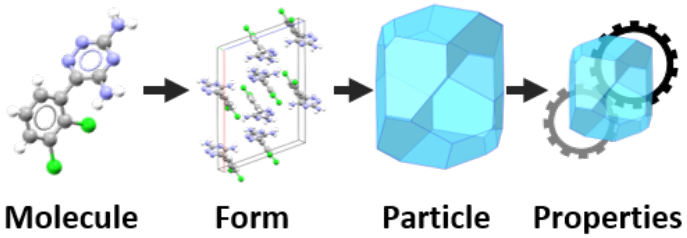
Chang Wang[1,2] · Ian Rosbottom[2] · Thomas D. Turner[2] · Sydney Laing[2] · Andrew G. P. Maloney[3] · Ahmad Y. Sheikh[4] · Robert Docherty[2] · Qiuxiang Yin[1] · Kevin J. Roberts[2]

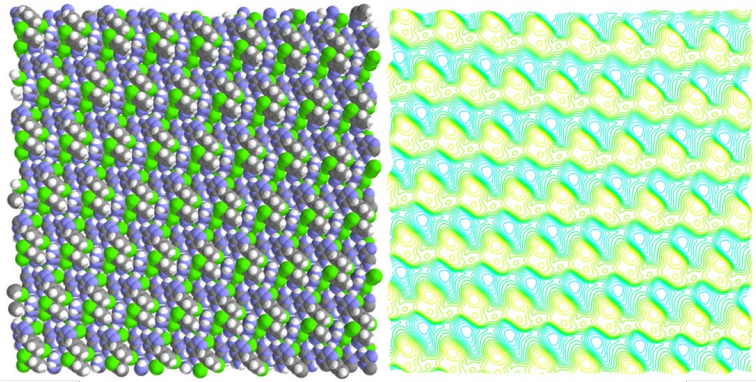






Digital Design Enabled Workflows – Particle Informatics





The {1, 1, 0} face of Lamotrigine displaying the chemistry of the surface

CRYSTAL GROWTH & DESIGN

Article

Cite This: *Cryst. Growth Des.* 2019, 19, 5258–5266

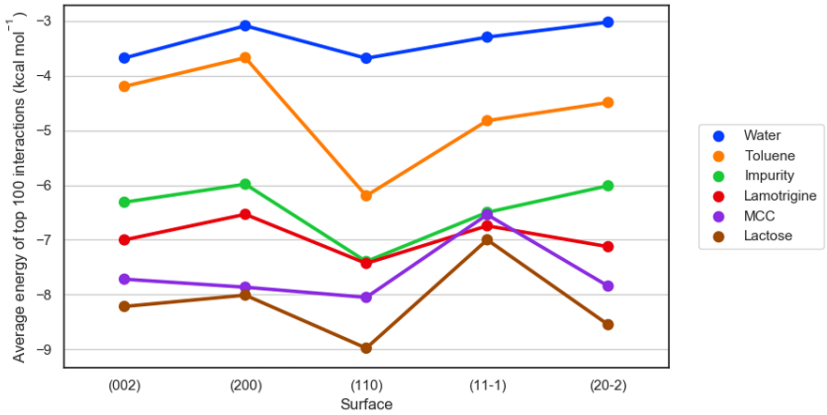
pubs.acs.org/crystal

"Particle Informatics": Advancing Our Understanding of Particle Properties through Digital Design

Mathew J. Bryant,[†] Ian Rosbottom,[‡] Ian J. Bruno,[†] Robert Docherty,[§] Colin M. Edge,[∥] Robert B. Hammond,[‡] Robert Peeling,[⊥] Jonathan Pickering,[‡] Kevin J. Roberts,[‡] and Andrew G. P. Maloney*[,†]

Building the formulation link

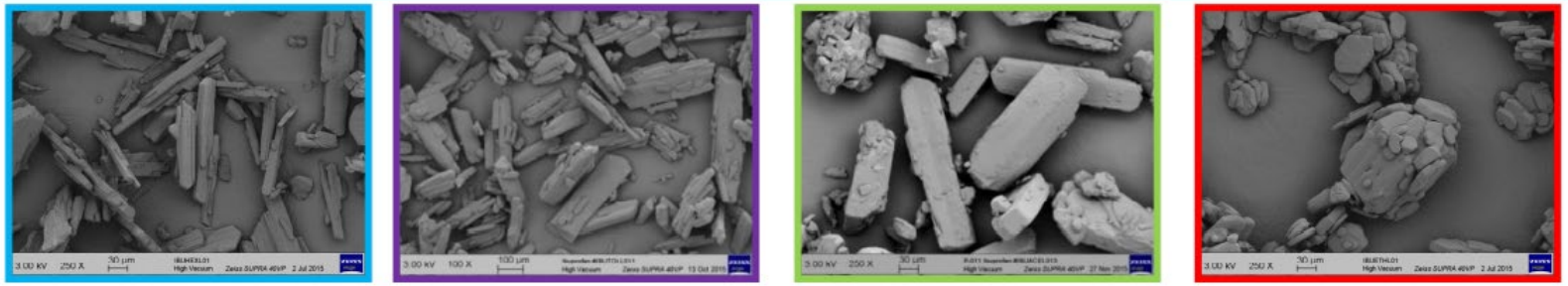
ADDoPT team effort with number of authors but important to acknowledge that Kendall Pitt provided the insight into the legacy Lamotrigine formulation selection and how challenges could be addressed with '*new*' workflows



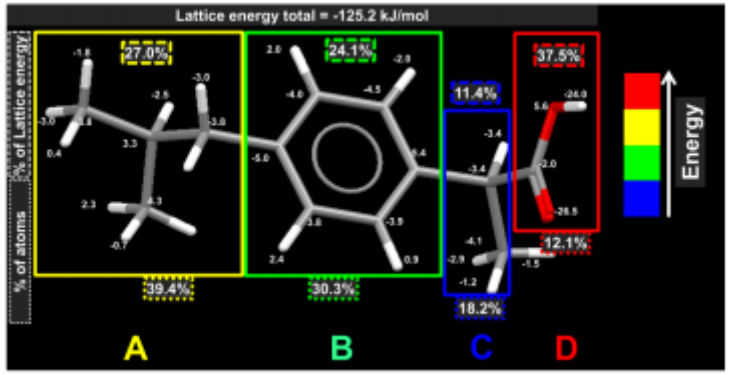
Average energy of the probe-surface interactions for the major surfaces of lamotrigine for water, toluene, dichlorobenzoic acid (impurity), Lamotrigine, microcrystalline cellulose (MCC), and lactose

Manufacturing - Digital Design Enabled Workflows
Sticking Propensity

Increasing aspect ratio



Increasing sticking propensity

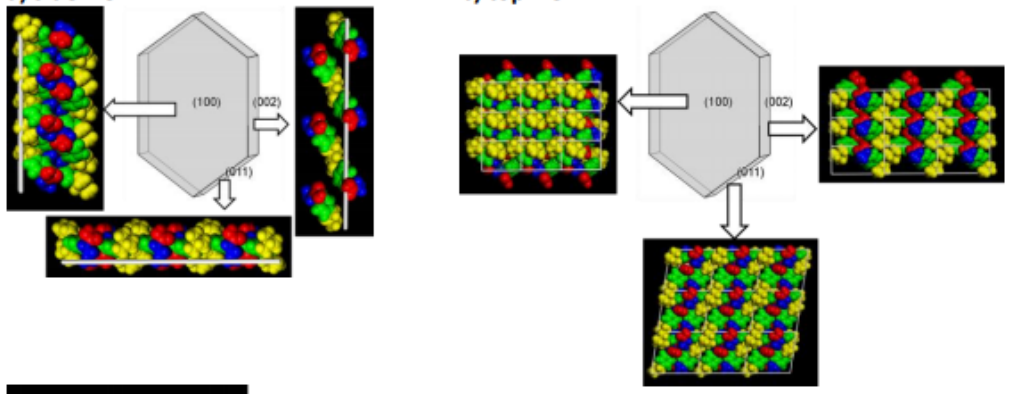


Classical Materials Sciences

A novel small scale sticking test was developed to help address sticking issues in support of manufacturing

a) side view

b) top view



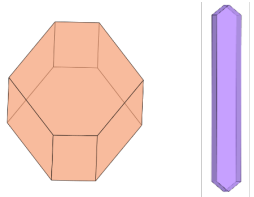
Effects of Crystal Habit on the Sticking Propensity of Ibuprofen—A Case Study

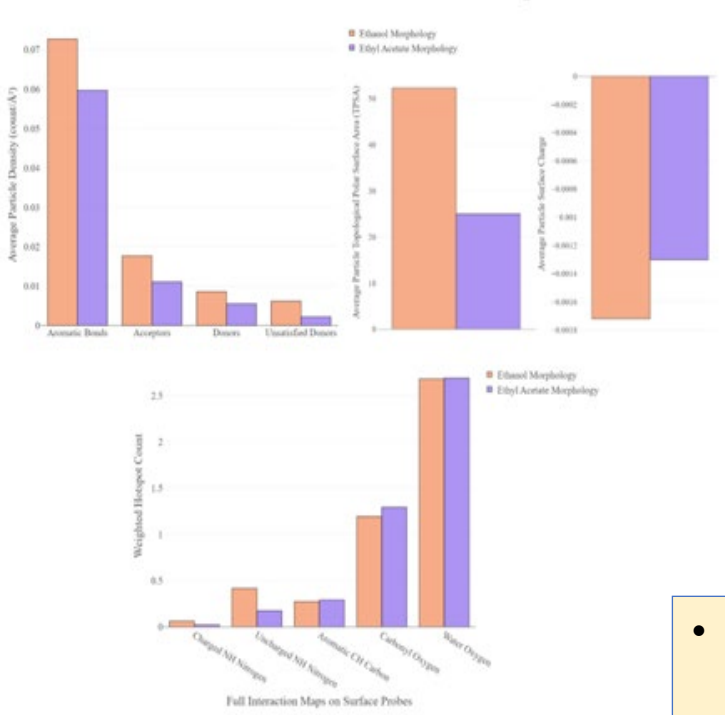
August 2017 · International Journal of Pharmaceutics 531(1)
DOI:10.1016/j.ijpharm.2017.08.091
Hooper, Clarke, Docherty, Snowden, Mitchell

Digital design for pharmaceutical product and process development (europeanpharmaceuticalreview.com)

Digital Workflows API: DP interface
Connecting Disciplines and Communities

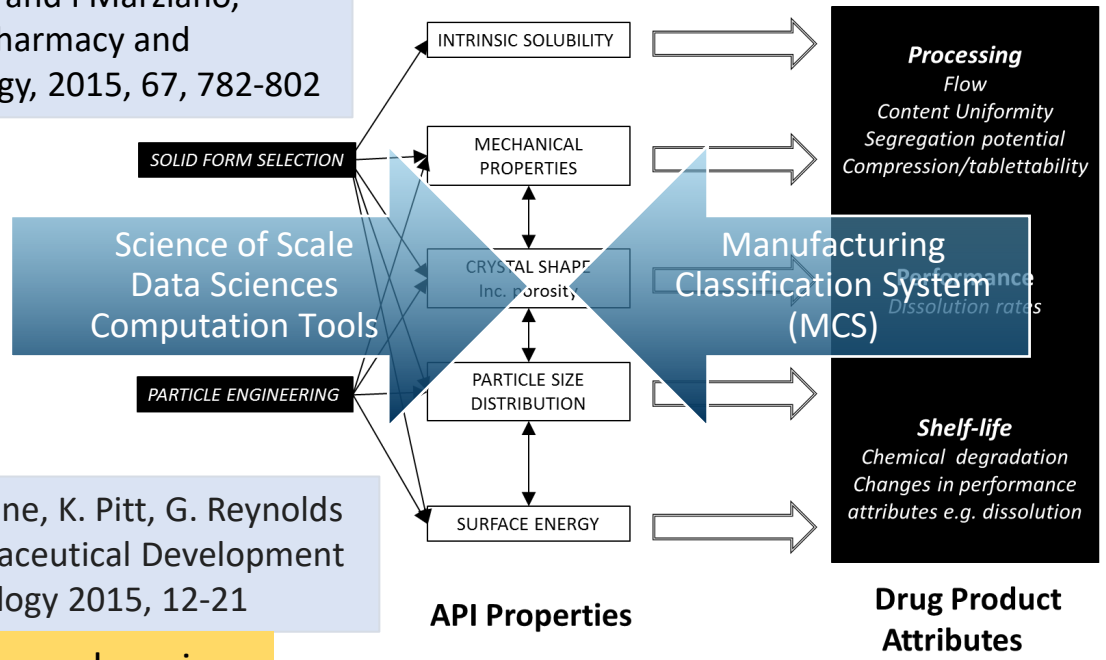
Particle Informatics





Institutional knowledge

M Ticehurst and I Marziano, Journal of Pharmacy and Pharmacology, 2015, 67, 782-802



MCS M. Leane, K. Pitt, G. Reynolds *et al* Pharmaceutical Development and Technology 2015, 12-21

Cross company learning

- Structural science at the interface between active pharmaceutical ingredient (API) and the formulated drug product (DP).
- A common language at the interface across the development disciplines
- Enables the science and understanding in development to be transitioned into manufacture allowing for effective product lifecycle management

Overview of Presentation

Short Questions and Answers Interlude at End of Each Section

Background and Context – Why

- Historical Importance of Materials Sciences
- Recent examples showing continued relevancy in Industry
- Recent examples showing continued interest and excitement in industry and academia

A historical review of the landscape over 15 years

- The changing demands form Industry on Materials Sciences
- Risks, benefits, and challenges of acceleration for solid form selection timings
- Examples of progress and Decision trees around solid form options

Fusing Experimental and Digital Workflows – How

- Examples of Structural Science, Solid Form Tools and Computational Methods
- Particle Informatics Vignettes
- Critical role for the structural tools in underpinning product acceleration

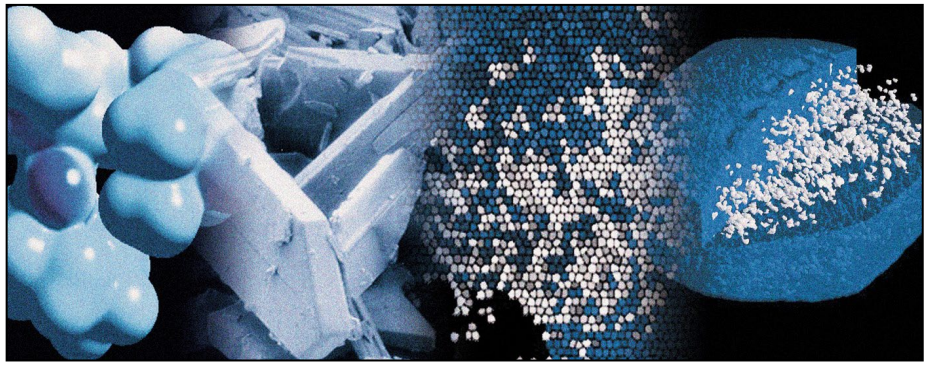
Future Outlook – Digital Design

- Re-shaping the Materials Sciences Knowledge Curve
- Digital Transformation, Digital Design and the Molecule to Medicine acceleration
- Crystallographic data as an integral digital thread through pharmaceutical development
- The CSD data trust opportunities partnering across Processing, Properties, Performance

Digital Design
Structural Data Integral to this Vision

- An unprecedented structural perspective of product design
  - Design products from the molecular structure upwards which assists troubleshooting and importantly allows us to build quality design concepts in *de novo.*
- Enhanced relationships at the academic/industry interface
  - We are developing a sophisticated scientific support ecosystem which complements our internal capabilities.
- Towards a digital definition of drug product and process design
  - We are evolving to use a digital framework for product design and process development which will revolutionise product realisation in terms of speed and quality.

'Towards Computational Product and Process Design'
The Royal Society, London, November 2014

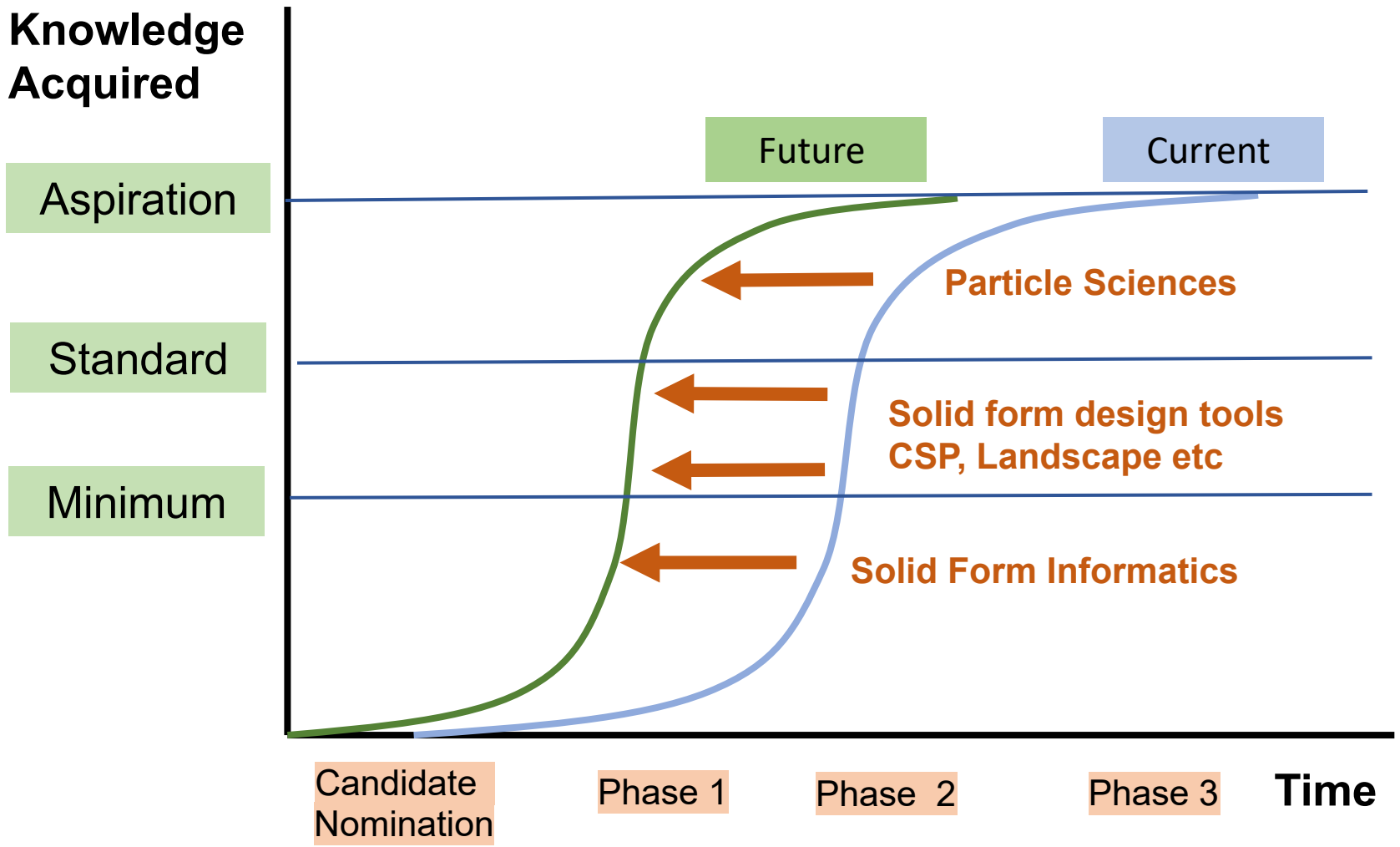


'Digital Design'
Medicines Manufacturing Industry Partnership (MMIP) Conference, Sandwich, June 2019

Select the right molecule → **Design the right product** → **Optimise the manufacturing processes**

The Materials Sciences Knowledge Curve

Adapted from Arden House presentation London, March 31st 2008 (B. Docherty)



Re-shape the knowledge curve.

More understanding earlier but not by simply burning more resources.

Deploy across the portfolio and target experiments for each candidate.

Efficiency Acceleration

The Importance of Crystallographic Studies. A Critical Data Thread Across Drug Development

Legacy
Why do we need one of them ?

Solid State Link to Properties
A combination of the molecular features and crystal packing allows understanding of key properties

Solid Form and Particle Sensitivity
Crystal structures can give early insight on sensitivity of product performance to variability.

Production Support
The crystallography is increasingly a foundational piece of data used in these studies to resolve issues across API:DP lifecycle.

Confirmation of Molecular Structure Single crystal X-ray diffraction structure the *'gold standard'*

Crystallization Understanding the crystallography helps define the choice of crystallization path (impurities, solvates)

Solid-State Long-Term Stability
Changes on processing and storage can result in changes to physical and chemical stability.

1 3 5 7 9 11

Discovery Phase 1 Phase 2 Phase 3 Registration Production

2 4 6 8 10 12

Confirmation of Crystal Packing of enabling Form gives the structural fingerprint connecting early characterisation

Formulation Composition
Selection of excipients may be influenced by interactions at surfaces of the API.

Solid State Focused Analytical Control
A well-characterized and understood crystal structure landscape underpins the analytical method.

Future
Talks tomorrow will capture the impact much more elegantly

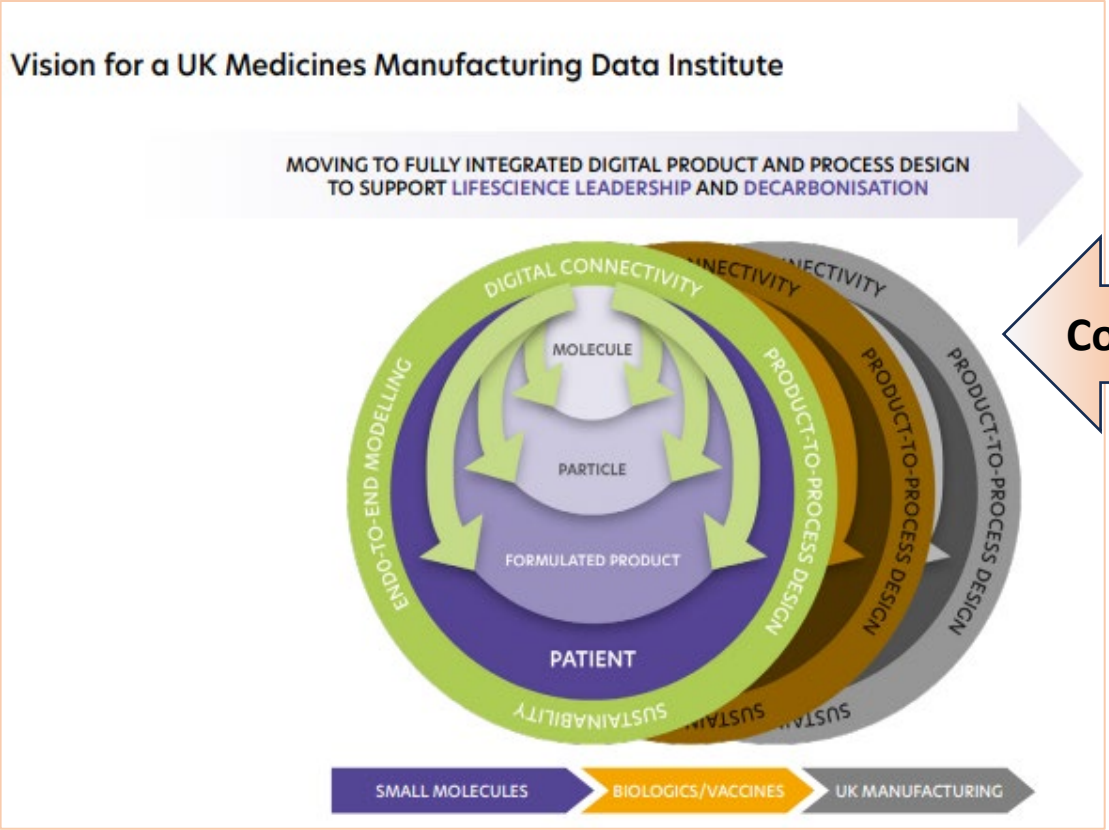
Solid Form Health Check
informatics approaches explore the stability of the current form relative to projections from the CSD *'knowledge bank'*

Process Optimization
Late changes in clinical studies (i.e., dose) may make product performance more sensitive to API material properties.

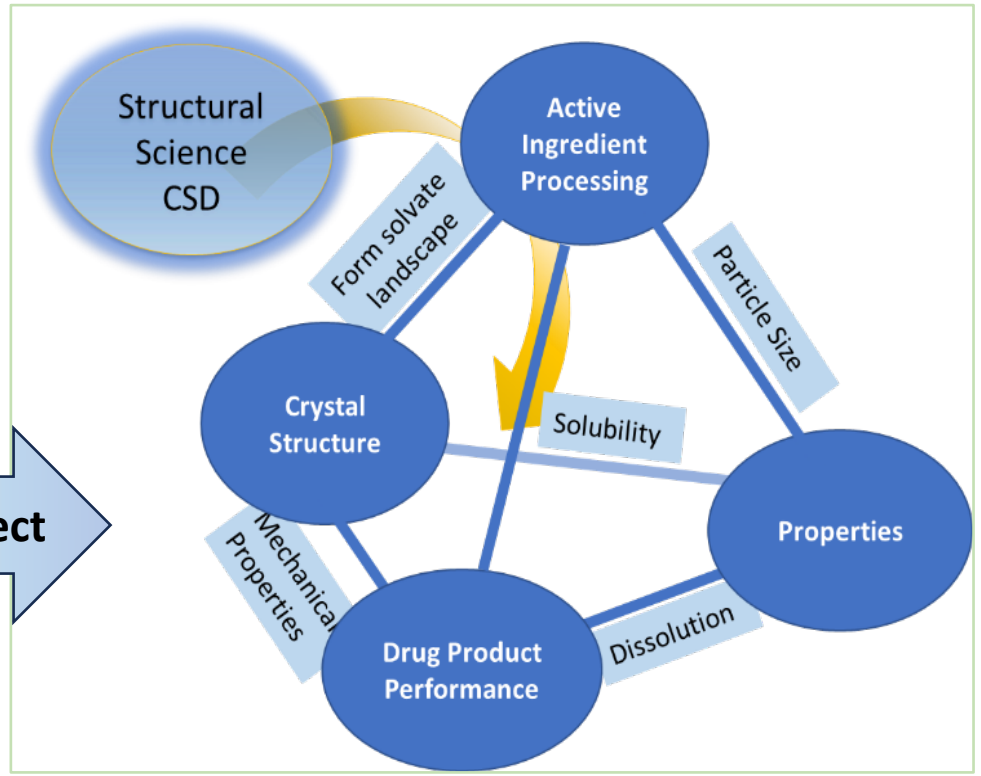
New Products Fusing of the potential solid-state landscape and patient needs can enable the development of product enhancement opportunities.

Towards Medicines Design and Manufacture
Embracing the Opportunity Over the Next Decade

Industry Needs: From the Medicine Manufacturing Industry Partnership - June 2023 Review



Connect



Scientific Opportunity: **T4**

Tapestry -around the crystallographic data thread
Technology - the scientific focus to connect
Translation – partnerships across all the disciplines.
Training – appropriate crystallographic awareness.

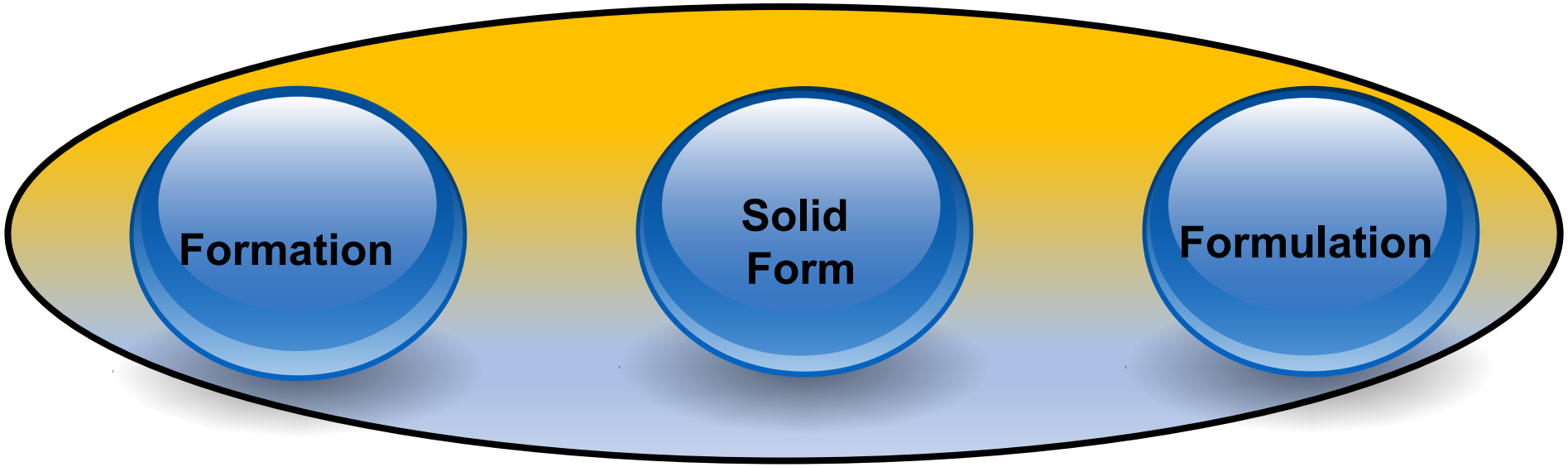
Tetrahedron adapted from C. Sun, J Pharm Sci 98, No. 5, May 2009

Summary

- The challenge for the medicinal chemist and pharmaceutical scientist in tackling the product design of highly complex new chemical entities remains a significant one due to:
    - Increasing molecular complexity resulting in a complicated solid form space that needs to be understood and evaluated.
    - Multiple conformational degrees of freedom can result in complex solid form structures and consequently significant barriers to crystallisation.
    - Different solid forms may have considerably different chemical or physical stabilities and biopharmaceutical properties as both an API and a drug product.
    - Anisotropic external particle morphologies with different crystal faces exhibiting different surface chemistry, and interactions with solvents and impurities.
- A clear understanding of solid form and particle attributes is critical to any accelerated product development strategies (i.e., Breakthrough Designation)
- A digital definition of the solid form and particle attributes is a critical thread in the digital tapestry that will make up the future molecule to medicine journey.

Pharmaceutical Properties—the Importance of Solid Form Selection Cheryl Doherty, Amy Robertson, Robert Docherty and Nicola Clear. Chapter 22, The Handbook of Medicinal Chemistry. Principles and Practice (Editors Andrew Davis, Simon E Ward) The Royal Society of Chemistry, Cambridge (2023).

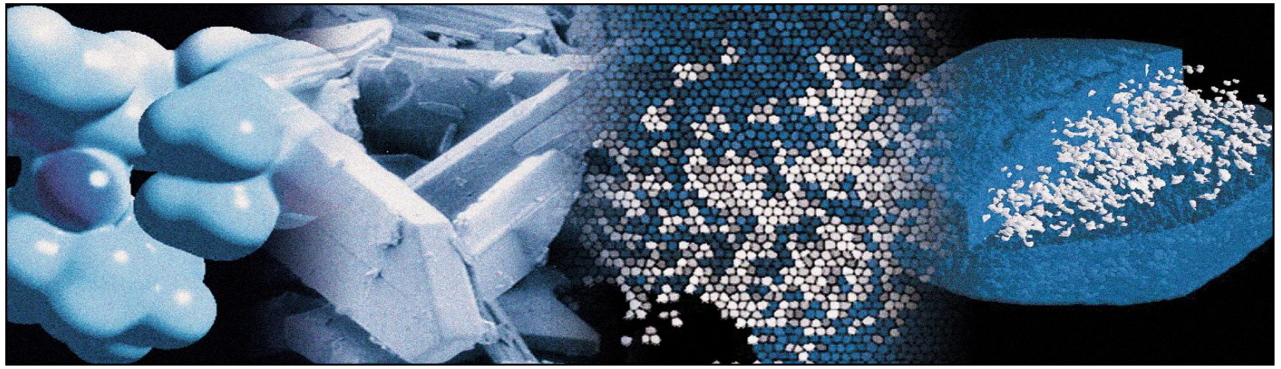
A Final Thought



CCDC Strategic Priorities

Data **Science** **Community** **People**

Discovery
API
Drug Product
Manufacturing



Tapestry
Technology
Translation
Training

Acknowledgements

- *The CFC for the last 15 years has been integral to help the Materials Sciences community become central to the molecule to medicine journey*
- *Going forward structural sciences will be foundational to the digital design transformation of that molecule to medicine journey.*
- *If the last 15 years have been about securing the '4th Discipline' maybe the next 15 years is about partnering and projecting the value of the Materials Sciences across the whole of development*

'All the means of action - the shapeless masses – the materials - lie everywhere about us. What we need is the celestial fire to change the flint into the transparent crystal, bright and clear.'

Henry Wadsworth Longfellow (1807 - 1882)

Pfizer Colleagues
ADDoPT Partners
MMIP community
Leeds University **CCDC colleagues**

Background References

- **Key References in Books**

Materials Science - Solid Form Design and Crystallisation Process Development, K. Roberts, R. Docherty and S. Taylor in *Pharmaceutical Process Development: Current Chemical and Engineering Challenges* ed. J. Blacker and M.T. Williams, The Royal Society of Chemistry, Cambridge (2011).

Pharmaceutical Properties—the Importance of Solid Form Selection Robert Docherty and Nicola Clear. The Handbook of Medicinal Chemistry. Principles and Practice (Editors Andrew Davis, Simon E Ward) The Royal Society of Chemistry, Cambridge (2014).

Pharmaceutical Properties—the Importance of Solid Form Selection Cheryl Doherty, Amy Robertson, Robert Docherty and Nicola Clear. Chapter 22, The Handbook of Medicinal Chemistry. Principles and Practice (Editors Andrew Davis, Simon E Ward) The Royal Society of Chemistry, Cambridge Feb 2023).

Engineering Crystallography: From Molecule to Crystal to Functional Form (Editors K.J. Roberts, R. Docherty and R. Temura) Springer VCH July 2017

- **Solid Form Selection**

A Theoretical Investigation of Conformational Polymorphism: (1) o-Acetamidobenzamide R. Docherty, M. Charlton, D. Buttar and J. Starbuck J. Chem. Soc. Perkin Trans 2. (1998) 763-772

The integration of solid-form informatics into solid-form selection Feeder, Neil; Pidcock, Elna; Reilly, Anthony M.; Sadiq, Ghazala; Doherty, Cheryl L.; Back, Kevin R.; Meenan, Paul; Docherty, Robert *Journal of Pharmacy and Pharmacology* 67(6), 857-868. (2015),

Low solubility in drug development: de-convoluting the relative importance of solvation and crystal packing Docherty, Robert; Pencheva, Klimentina; Abramov, Yuriy A. *Journal of Pharmacy and Pharmacology* 67(6), 847-856 (2015),

Impact of Crystal Structure and Molecular Conformation on the Hydration Kinetics of Fluconazole Basford, Patricia A, Back, Kevin R, Cram, Michael, Docherty Robert, Davey, Roger J, Cruz-Cabeza, Aurora J. Crystal Growth & Design (2019), 19(12), 7193-7205

The CSD Drug Subset: The changing chemistry and crystallography of small molecule pharmaceuticals M. Bryant, S. Black, H. Blade R. Docherty, A. Maloney, S. Taylor, J. Pharm. Sciences (2019), 108(5), 1655-1662.

Background References

- **Particle Sciences**

Synthonic Engineering: From molecular and crystallographic structure to the rational design of pharmaceutical solid dosage forms Roberts KJ, Hammond RB, Ramachandran V, Docherty R (2016) in *Computational Approaches in Pharmaceutical solid state chemistry,* Editor: Abramov YA., Wiley, Chichester, UK

Particle Informatics: Advancing our Understanding of Particle Properties Through Digital Design Bryant, Mathew J.; Rosbottom, Ian; Bruno, Ian J.; Docherty, Robert; Edge, Colin M.; Hammond, Robert B.; Peeling, Robert; Pickering, Jonathan; Roberts, Kevin J.; Maloney, Andrew G. P. *Crystal Growth & Design (2019), 19(9), 5258-5266.*

Molecular, Solid-State and Surface Structures of the Conformational Polymorphic Forms of Ritonavir in Relation to their Physicochemical Properties' Chang Wang, Ian Rosbottom, Thomas D. Turner, Sydney Laing, Andrew G. P. Maloney, Ahmad Y. Sheikh, Robert Docherty, Qiuxiang Yin & Kevin J. Roberts Pharmaceutical Research (2021), 38, 971–990

- **Digital Design Transformation**

European Materials Modeling Council: The EMMC Roadmap for Materials Modelling, V3.0.2, first release on 2015.2.26, Accessed via: http://emmc.info/roadmap/

ADDoPT Case Studies https://www.addopt.org/news/latest_news/case_studies/

Digital Design Docherty, R The Medicines Manufacturing Industry Partnership (MMIP) Conference, Sandwich, June, 2019

Digital Design: Docherty R **,** Bionow Pharma Manufacturing Conference , Virtual Conference May 2021

Background References

- **Literature/Community Landscape slides**

Strategies for Managing Solid Form Transformation Risk in Drug Product. U. Kestur, A. Patel *et al* J. Pharm. Sciences (2023) 112, 4, 909

Co-crystal of Tramadol Hydrochloride–Celecoxib (ctc): A Novel API–API Co-crystal for the Treatment of Pain C. Almansa, R. Mercè, *et al* Cryst. Growth Des. 2017, 17, 4, 1884–1892

Differential Solution Behavior of the New API–API Co-Crystal of Tramadol–Celecoxib (CTC) versus Its Constituents and Their Combination A. Port, *et al* , Cryst. Growth Des. 2019, 19, 6, 3172–3182

Polymorphs and isostructural cocrystals of dexamethasone: towards the improvement of aqueous solubility R.B. Varsa, P. Sanphui and V. Chernyshev CrystEngComm, 2022,24, 6045-6058

Two polymorphs of remdesivir: crystal structure, solubility, and pharmacokinetic study K. Yu, *et al* CrystEngComm, 2021,23, 2923-2927

Dapsone Form V: A Late Appearing Thermodynamic Polymorph of a Pharmaceutical D. E. Braun, M. Vickers, and U J. Griesser Mol. Pharmaceutics 2019, 16, 7, 3221–3236

Computational polymorph screening reveals late-appearing and poorly-soluble form of rotigotine. Mortazavi, M., Hoja, J., Aerts, L. *et al.* Commun Chem 2, 70 (2019)

Polymorphism in phenobarbital: discovery of a new polymorph and crystal structure of elusive form V S. Roy, N. Rajesh Gouda and A. J. Matzger Chem. Commun., 2016, 52, 4389-4392

Ritonavir Form III: A New Polymorph After 24 Years X. Yao , R.F. Henry and Geoff, G.Z. Zhang Journal of Pharmaceutical Sciences 112, Issue 1, January 2023, Pages 237-242

Ritonavir Form III: A Coincidental Concurrent Discovery S. D. Parent, et al Crystal Growth & Design 2023 23 (1), 320