Optiform™ Technologies – A Fit-for-Purpose Solution to Solid-State Issues

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DEVELOPMENT DELIVERY SUPPLY

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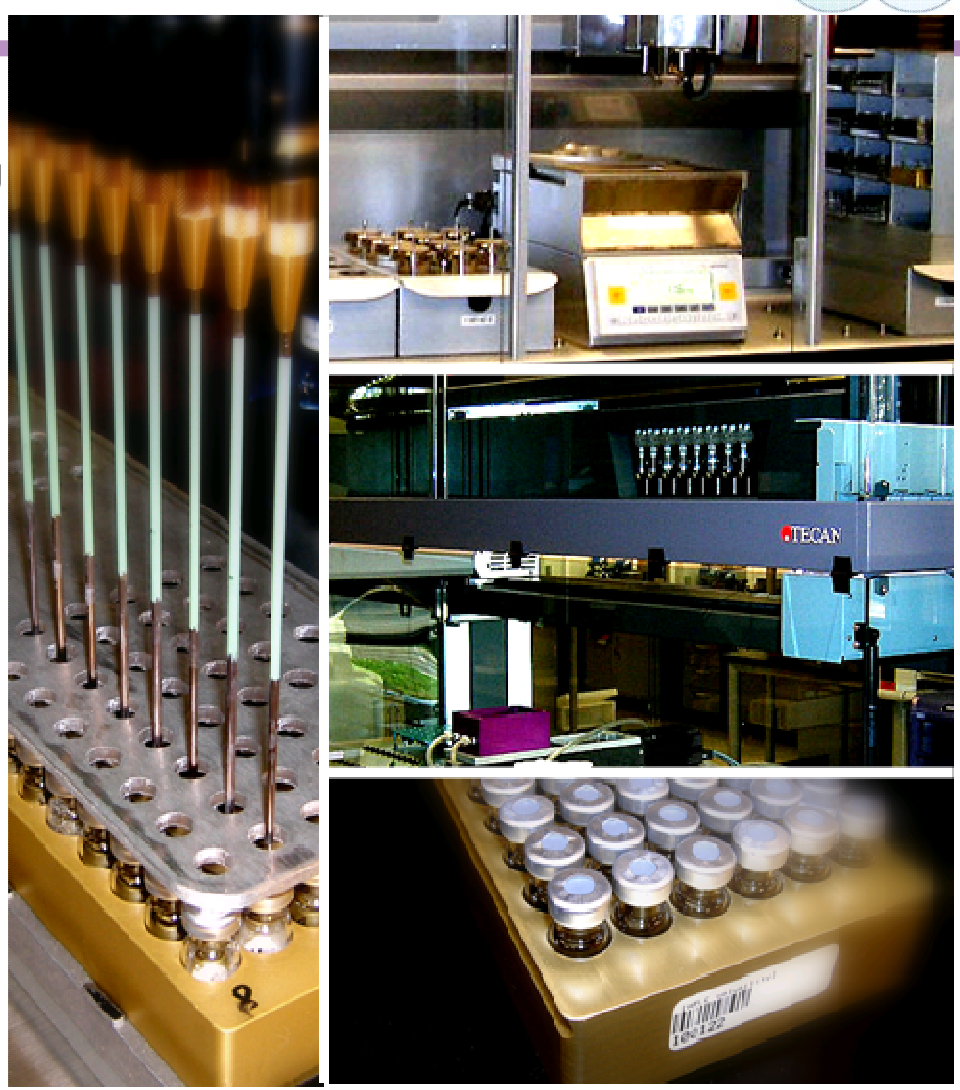
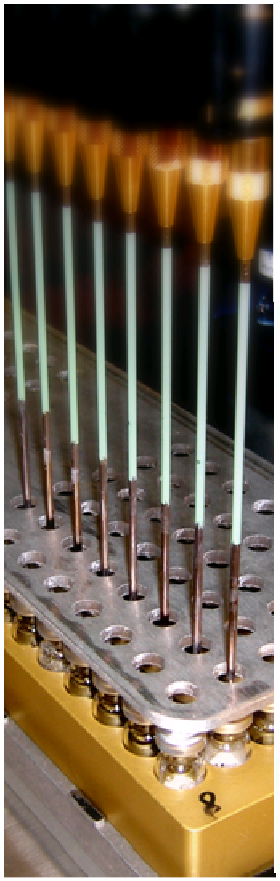
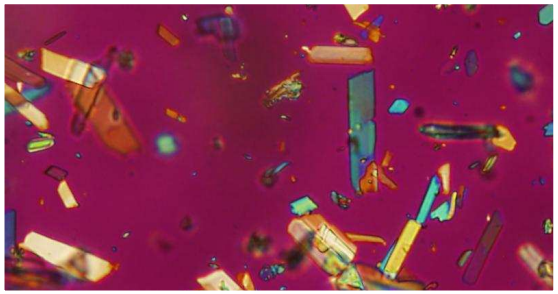
Optiform™ Technologies

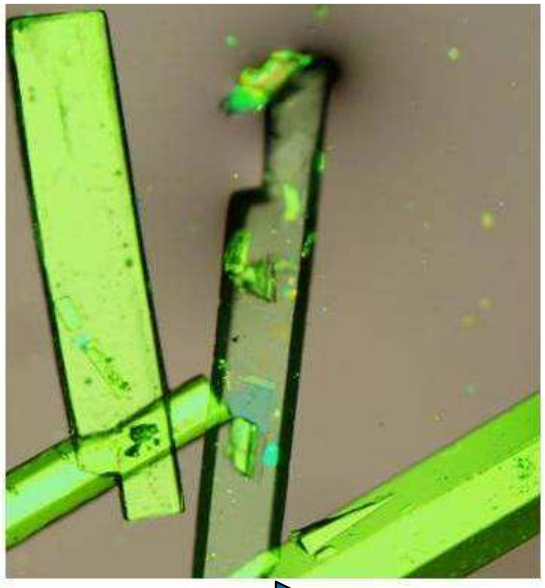
- **High-throughput platform for salt, crystal-form, and cocrystal screening**
- **Developed and refined over the past ten years within GlaxoSmithKline**
- **Applied to more than 500 compounds, spanning from early stage lead compounds through launched products**
- **Team of scientists with diverse backgrounds**
  - Analytical Chemistry
  - Synthetic Chemistry
  - Physical Chemistry
  - Materials Science
  - Crystal Engineering
  - Pharmaceutical Sciences
  - Automation and Software Development



Optiform™ Technologies







- *High-Throughput Platform*
- *Proven Screening Workflows*
- *Material Efficient*

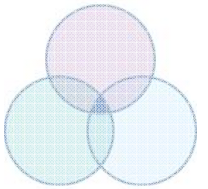
Optimizes API Performance

Enables Robust Manufacturing

Enhances Profitability

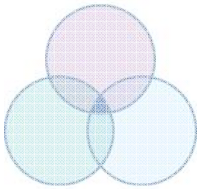
Faster to Market

Optimized API Performance



- Increase solubility - optimized *in-vivo* performance - speeds assessment of safety and efficacy
- Optimized shelf-life; Stability
- Hygroscopicity
- Particle attributes – shape/habit and size-distribution
- Bulk attributes – density and flow

Enabling Robust Manufacturing Operations



Drug Substance/API

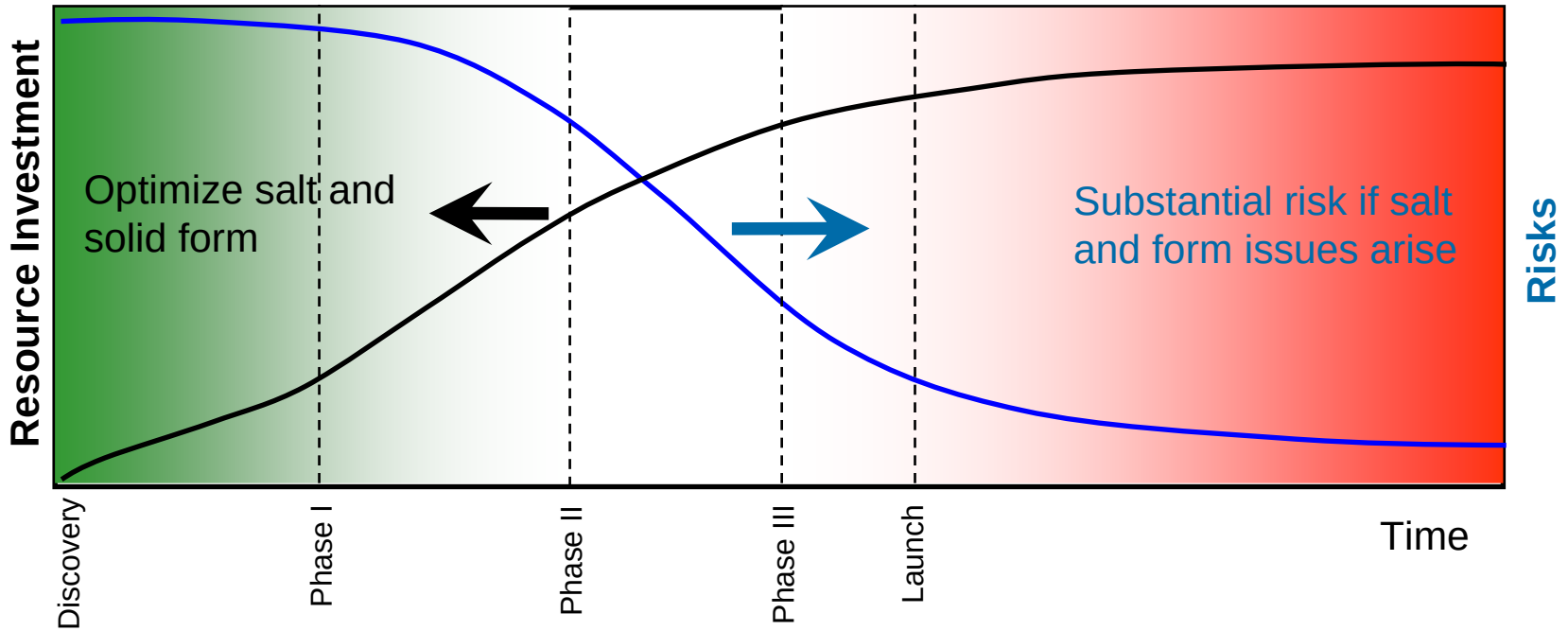
- **Consistent production of suitable/stable salt.**
- **Knowledge of form space enables design of more reliable crystallization processes.**
  - Avoiding problematic forms
  - Operating in a region where desired form is most-stable
- **Optimized yield and purity.**

Drug Product

- **Salt and crystal-form compatible with formulation.**
- **Salt and form stable during manufacturing operation (e.g., compression, wet-granulation)**

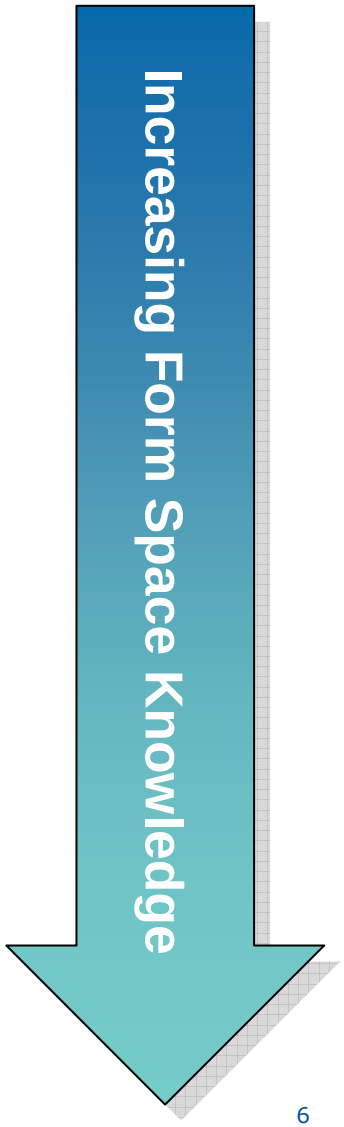
Enhancing Profitibility - Reducing costs and risks

- **Product development usually costs 30-35% of overall cost of developing a drug**
- **Optimizing salt and form early in the development process can significantly reduce potential risks and contribute to overall cost savings**



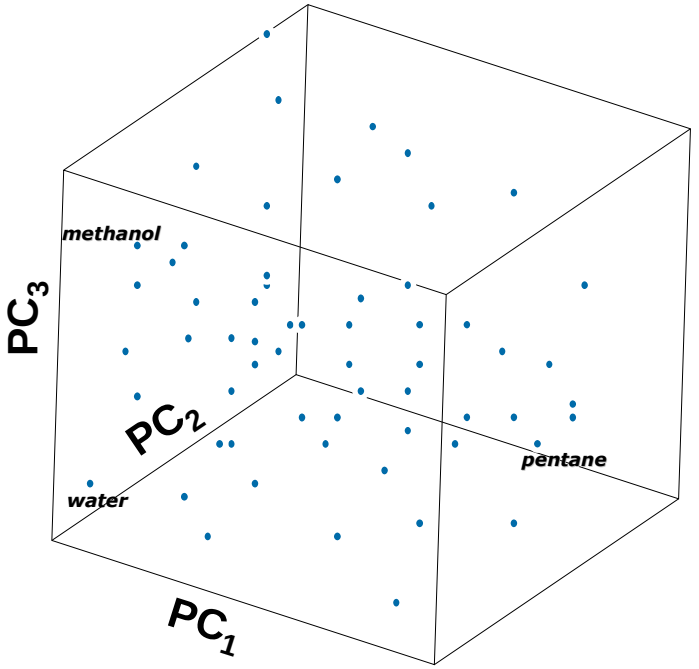
Crystal Form Screen

Stage	Development Goal
EARLY **(Lead to Candidate Selection)**	**Lead optimization and selection** • Crystallizing previously amorphous material (to support PK/BA assessment). • Produce crystalline material to enable purification and isolation. • Cursory glance at crystal-form space
MID **(Prior to DRF, 28 day GLP tox, FTIH studies)**	**Early Development** • Discovery of important crystalline forms (e.g., anhydrous, hydrated, and solvated). • Assessing form-relationships (e.g., kinetic and thermodynamic) • Recommend suitable form for development. • Evaluate impact on bioavailability and formulation
MID-LATE **Post-FTIH**	**API and Drug Product Process Development** • Identify and evaluate forms that may present risk to process (e.g., forms stable at process temperatures and conditions; metastable forms) • Perform risk-assessment employing metastable forms (e.g., seeding studies)
LATE **(post-POC, Phase II)**	**Process and IP Protection** • Comprehensive evaluation of form space • Process risk-assessment. • Identifying product line extension opportunities • Evaluate and strengthen intellectual property



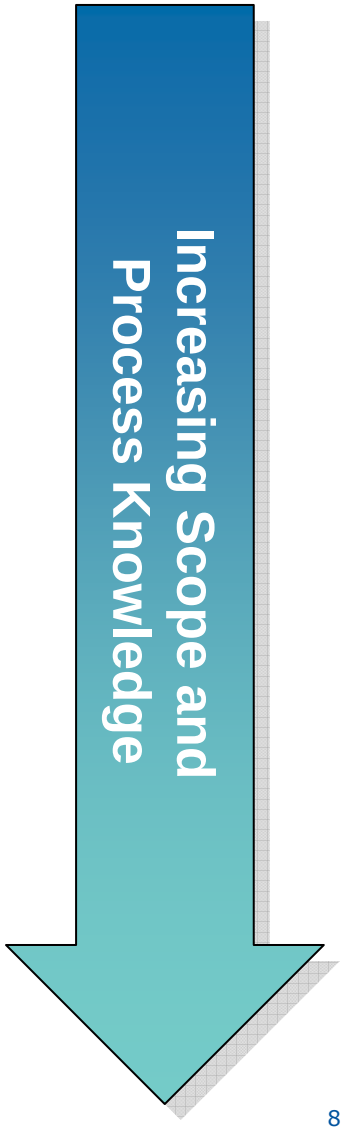
Crystal Form Screen Design Strategy

- **Rigorous experimental design that is customizable for each API.**
- **Predicted solubility to achieve a diverse solvent set in the design.**
- **Variety of high-throughput crystallization modes:**
  - Thermal treatment
    - Isothermal
    - Cycling
  - Cooling
  - Evaporative
  - Antisolvent Addition
  - Vapor Diffusion



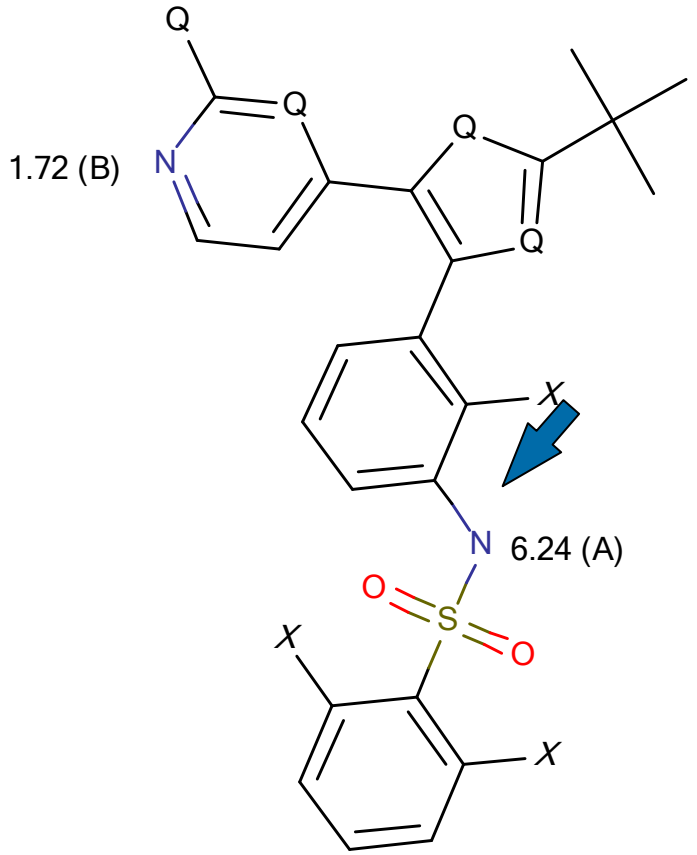
Salt Screening

Stage	Development Goal
EARLY **(Lead to Candidate Selection)**	**Lead optimization and selection (material limitations)** • Enhancing solubility/bioavailability to support PK and tox studies. • Optimize physical properties. • Optimize developability attributes (e.g., stability, hygroscopicity, dosing compatibility).
MID **(Prior to DRF, 28 day GLP tox, FTIH studies)**	**Early Development** • Optimized salt form identified to support DRF and GLP tox. • Compatible with FTIH formulation. • Can be reproducibly obtained from API process.
LATE **(post-POC, Phase II)**	**API and Drug Product Process Development** • A salt decision may be revisited if the existing salt proves too problematic to progress or a new formulation is required.
LAUNCH	**IP Protection** • A careful evaluation of the salt should be done around the time the product is going to be launched to ensure that relevant IP is protected. • Exploration of possible product line extension should also commence. This may require a more thorough salt screen



Salt Screen Design Strategy

- The chemical structure and pK_a of the parent are inspected
- Solubility and stability at different pH values & in different organic solvents are assessed
- The details of the formulation design such as route of administration, projected human doses, desired dosage form are used to direct the selection of counter-ions that will be employed



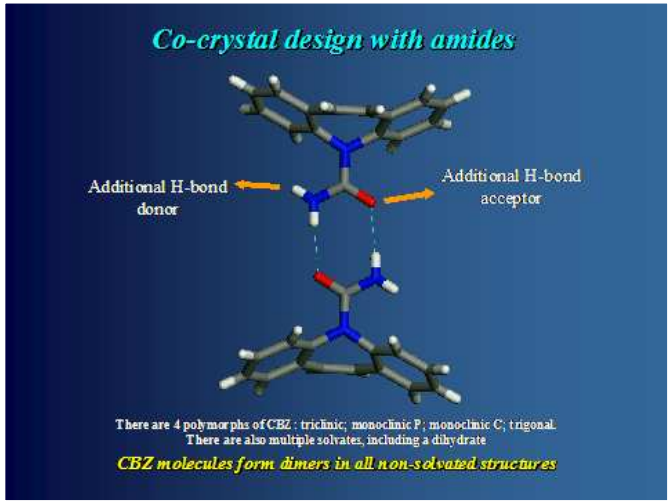
Cocrystal Screening and Design Strategy

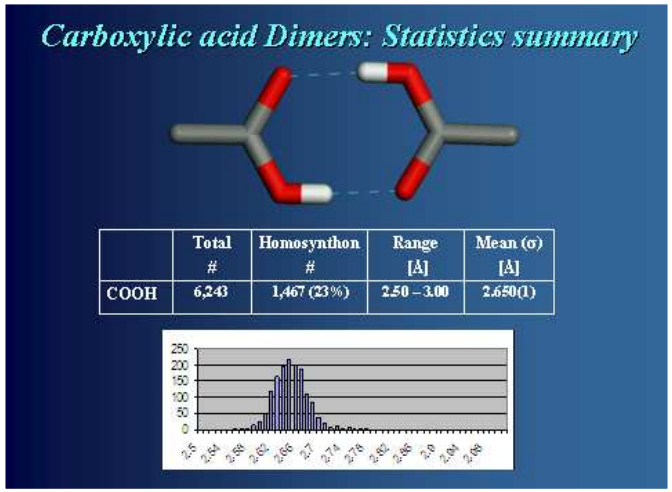
Strategic

- **Provides an option for enhancing kinetic solubility and increase in BA**
- **Applicable to non-ionizable and ionizable compounds and salts**
- **Opportunities for lifecycle management.**

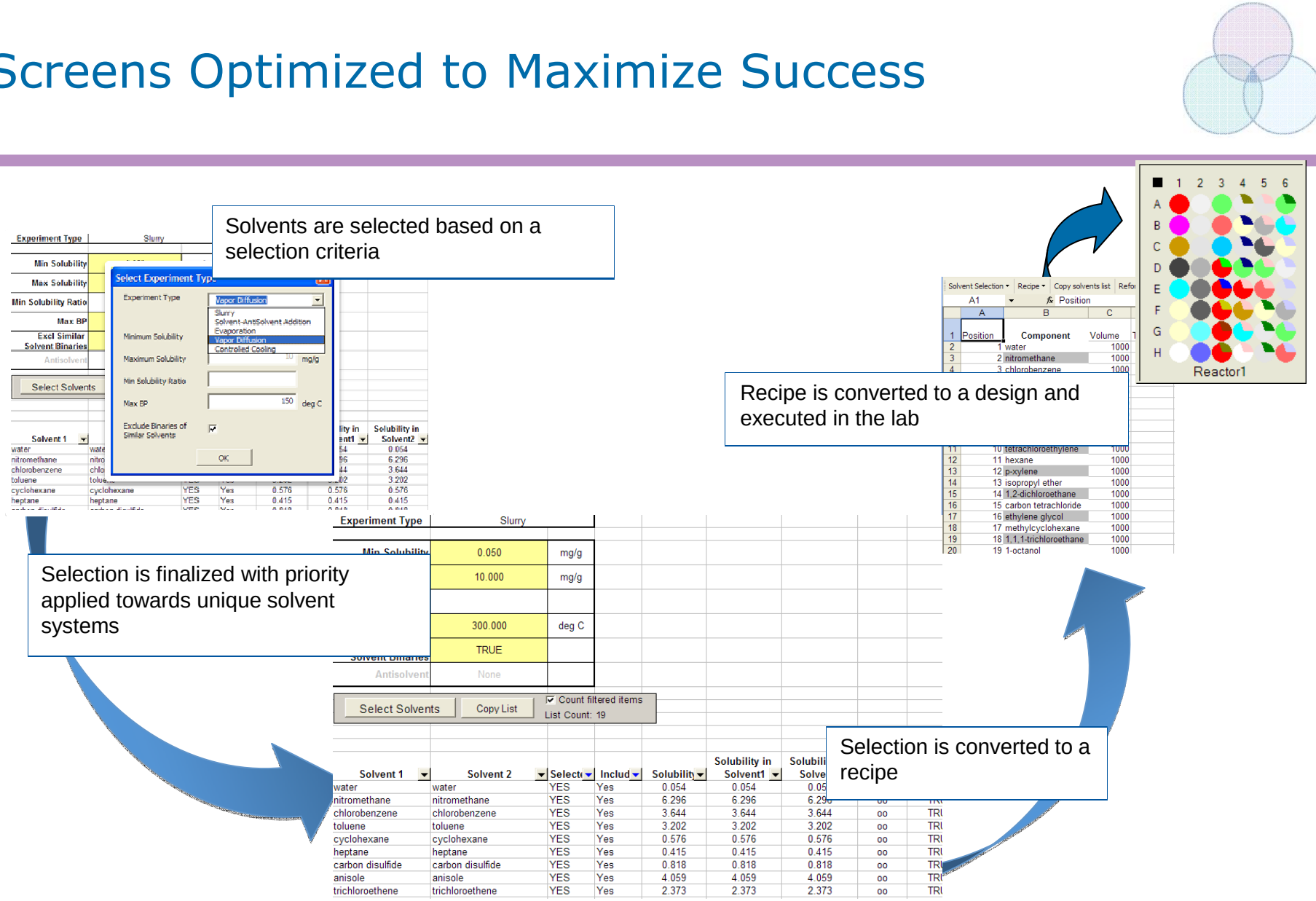
Technical

- **Literature data and queries in structural databases can advise on potential for forming stable structural motifs**
- **Various approaches (e.g., solvent-drop grinding, evaporation) have shown effectiveness in inducing cocrystallization**
- **Manual and high-throughput modes**





Screens Optimized to Maximize Success



Seamless interface between design and execution.

Computationally Assisted Data Analysis and Visualization Enhances Speed

Processing

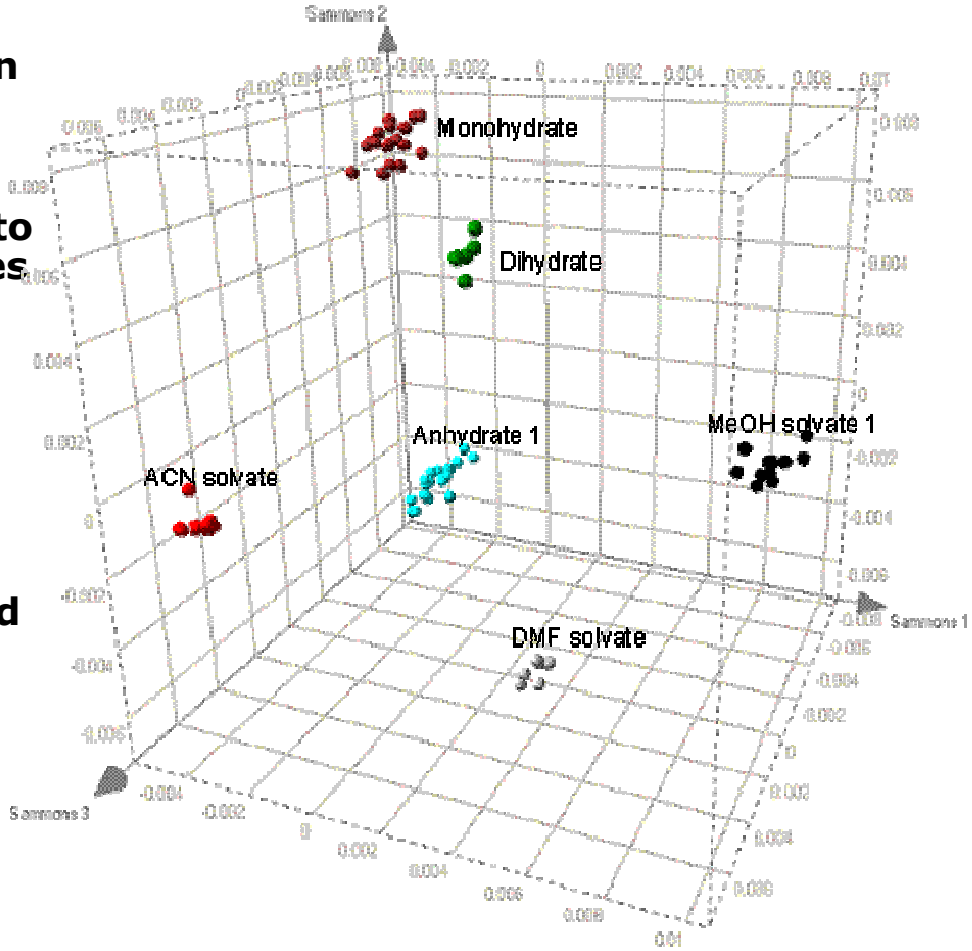
Initial clustering and sorting of FTRaman spectra is primarily using unsupervised clustering algorithm. The custom tool utilizes multivariate principal component analysis (PCA) to distinguish subtle spectral differences

Visualization

Clusters created in the initial step are visualized and closely inspected to reveal the relationships between samples

Validation

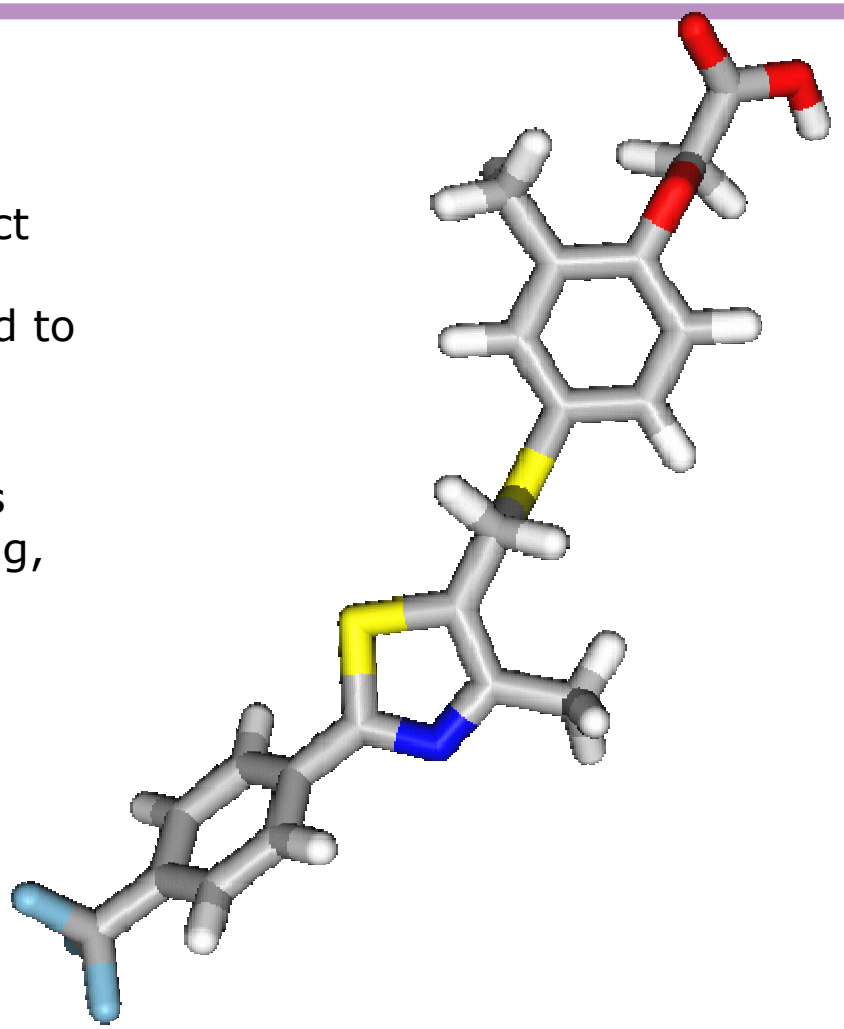
Representatives of clusters are identified for 2nd tier analysis



Case Study: Crystal Form Screen

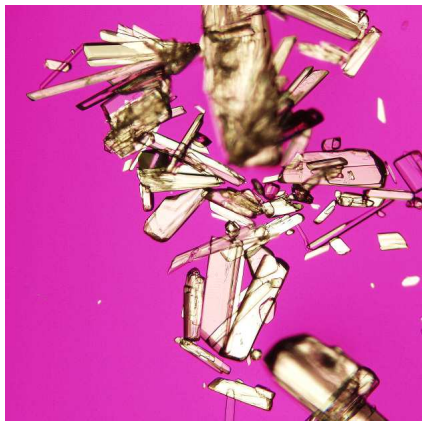
Objective: Examine form space of an API with moderate flexibility and MW

- API has several heteroatoms that can act as H-bond donors and acceptors thus propensity for polymorphism is expected to be high
- Screen was performed using 48 solvent systems and three crystallization modes (thermal treatments/temperature-cycling, evaporation, rapid cooling)

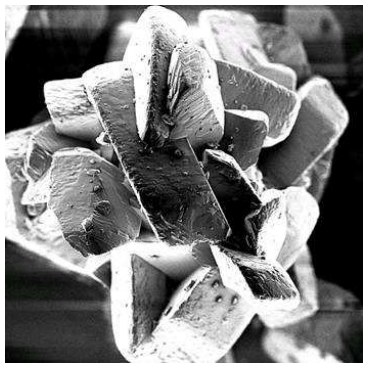


Case Study: Crystal Form Screen

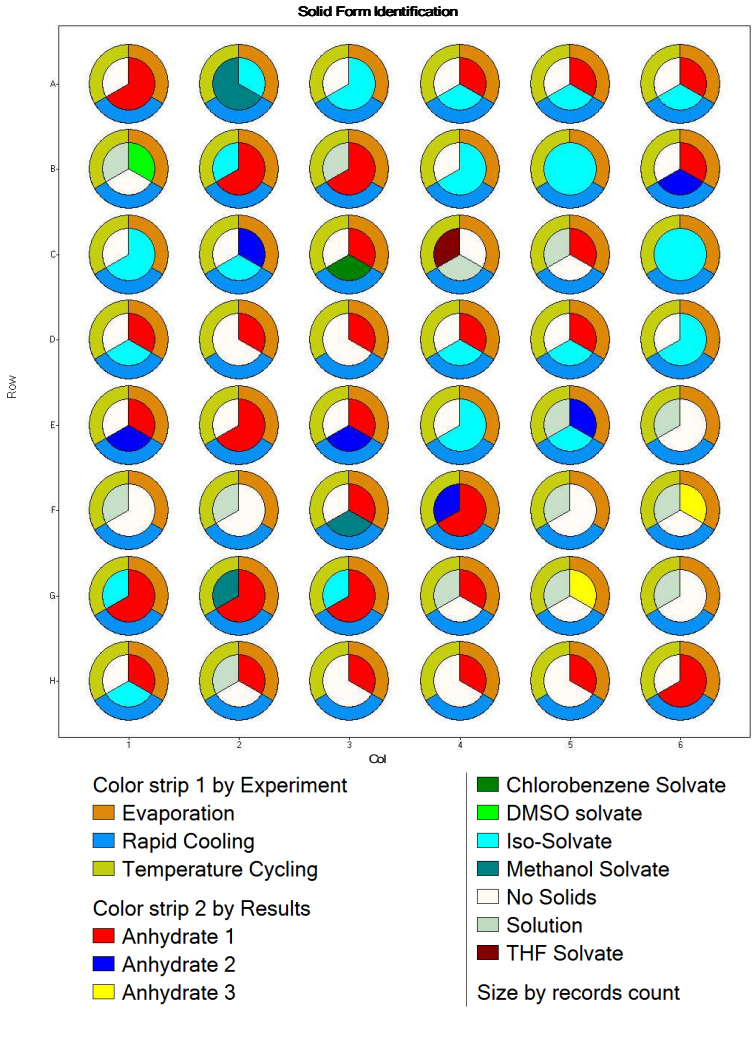
- **Several non-solvated forms discovered**
- **Series of isostructural solvates as well as distinct solvates have also been obtained**



DMF solvate (Isostructural Solvate)



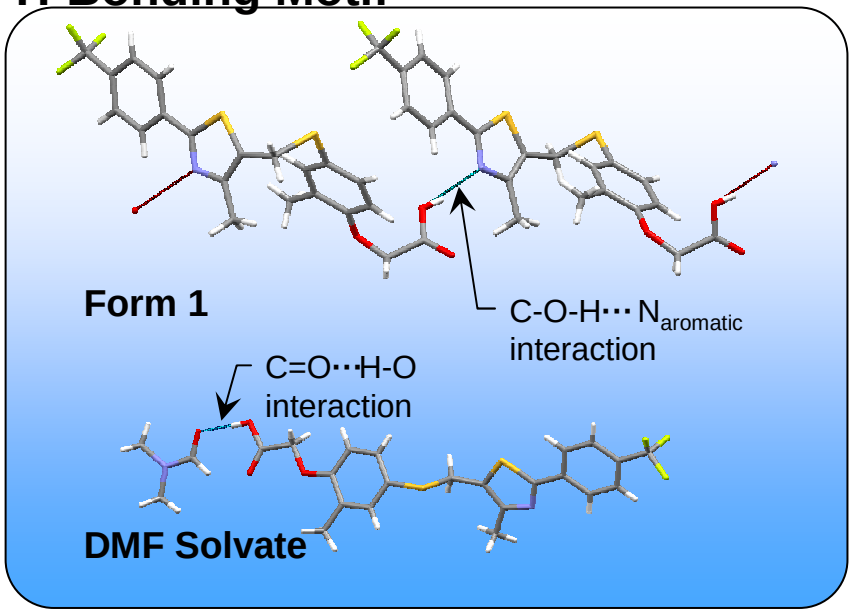
Form 1 (non-solvated)



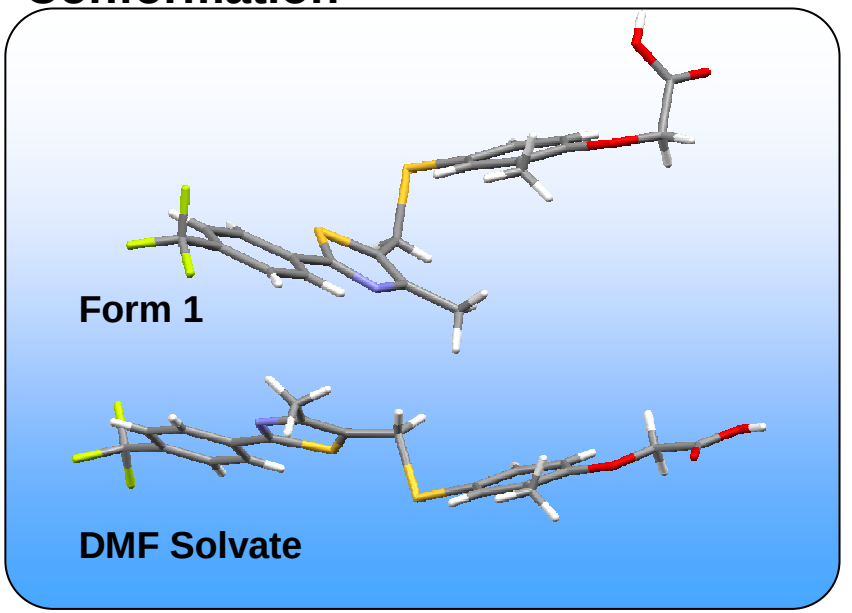
Case Study: Single Crystal Structures

- **<u>Form 1</u> - intermolecular H-bonding motif involving C-O-H···N(aromatic) interaction.**
- **<u>DMF solvate</u> - C=O···H-O interaction replaces H-bonding motif**
- **The propensity for H-bonding could explain the occurrence of several solvates involving solvents that can interact via H-bonds.**

H-Bonding Motif



Conformation



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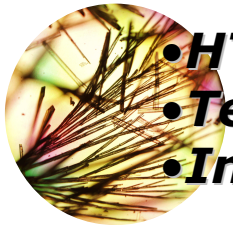

- ***HT platform for salt, crystal-form, and co-crystal discovery***
- ***Team of diverse and experienced scientists***
- ***Industry-proven workflows***

Catalent

discover more.

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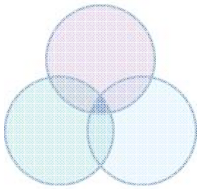
Instrumentation



- **X-Ray Diffraction**
  - PanAnalytical X ' Pert Pro Diffractometer
    - Variable temperature and humidity capabilities
    - Multi-sample
  - Bruker D8
    - with area detector for automated well-plate analysis
- **Vibrational Spectroscopy**
  - 3 Thermo-Nicolet FT-raman benches with micro-sampling capabilities
  - Mid-IR spectrophotometers for ATR, thermogravimetric and microspectroscopy applications
  - Dispersive raman spectrophotometer for microspectroscopy
- **Thermal Analysis Equipment**
  - Differential scanning calorimeters with modulated capabilities
  - Thermogravimetric analysis with inline mid-IR analysis
- **Dynamic Vapor Sorption Analysis**
  - Multiple sample parallel operation
- **HPLC**
- **Lyophilizers** (up to ~10g)
- **Scales of operation** (up to 1L)

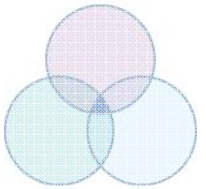
- **Microscopy**
  - Polarized light microscopes with hot-stage
  - Stereoscopes
- **Automated Sample Preparation**
  - Tecan®,[1] liquid-handling robots
  - Symyx/Autodose powder handling robots
  - Custom automation tools

- **Access to Catalent network**
  - Multi-nuclear NMR
  - Hyphenated mass spectrometric techniques
  - Dissolution testing
  - Formulation options to address unmet needs (Zydis® and Soft-gel capsules)

- **Access to offsite instruments**
  - Electron microscopy
  - Single crystal diffractometer

1 Tecan is a registered trademark of Tecan Group AG Corp.

Software



- **Symyx®,[1] Automation Suite**
  - Primarily used for designing and executing high-throughtput screens
  - Custom widgets to enable custom workflows
- Aspen Properties®,[2]
  - Solubility prediction via NRTL-SAC is incorporated in the crystal-form design
- Data Analysis Suites
  - Utilized for multivariate analysis and visualization of screening data

- Symyx is a registered trademark of Symyx Solutions, Inc.
- Aspen Properties is a registered trademark of Aspen Technology, Inc.

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