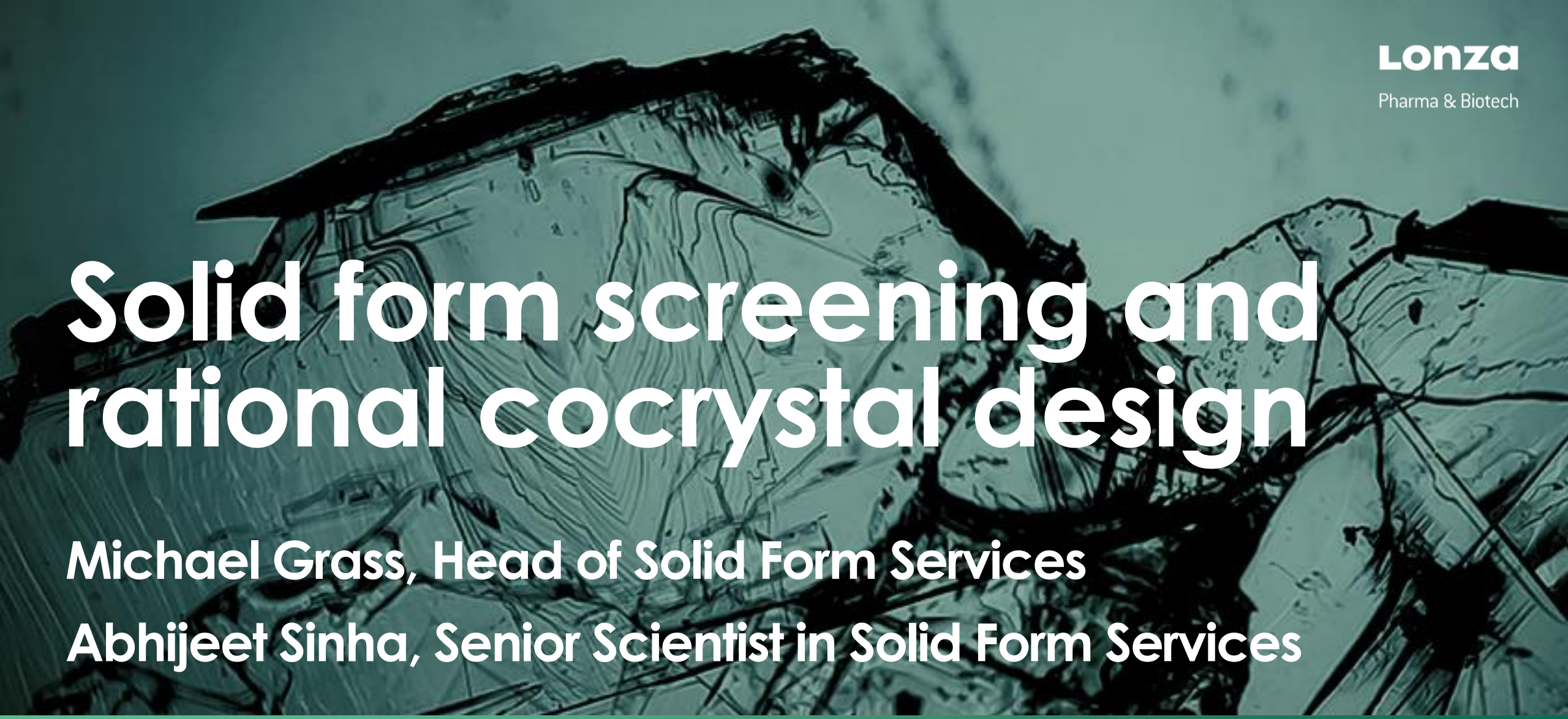


Lonza
Pharma & Biotech

Solid form screening and rational cocrystal design

Michael Grass, Head of Solid Form Services
Abhijeet Sinha, Senior Scientist in Solid Form Services

Small molecule technologies

Flexible model across the product development cycle

Lonza
Pharma & Biotech

DESIGN
Small / Lab-Scale (non-GMP) feasibility

DEVELOP *> 350Projects*
Clinical scale development, manufacture & packaging

MANUFACTURE *> 270 Products*
Commercial scale manufacture & packaging

Drug Substances

full range of API inclusive of GMP intermediates, HPAPI, cytotoxic payloads for ADC's

Particle-Engineering

micronization, amorphous solid dispersions, melt-spray-congealing

Drug Products

tablets (IR and MR), encapsulated powder & MP, soft gels, liquid-fill hard caps

SimpliFiH® Solutions – rapid first-in-human services

Designed for poorly soluble molecules and accelerated development

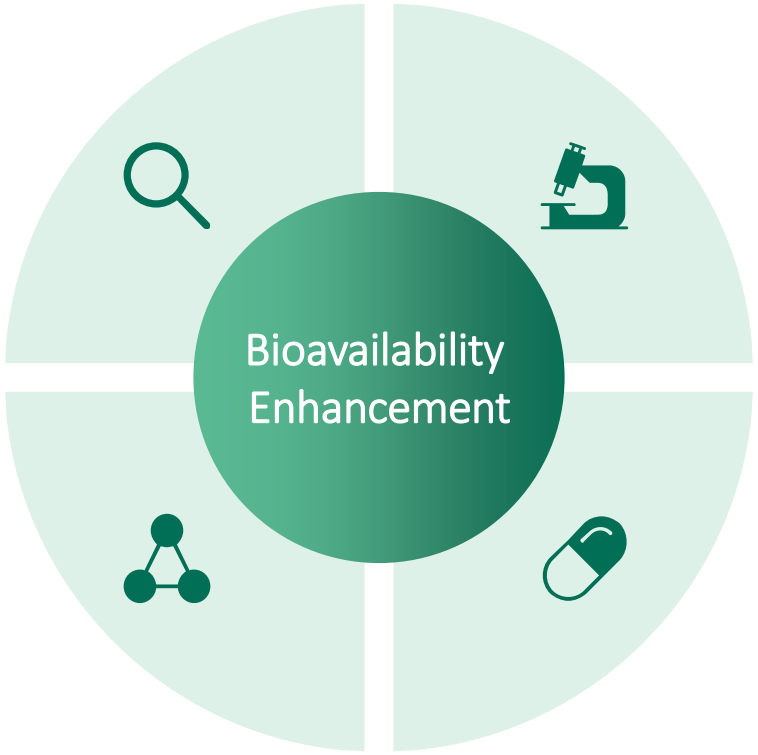
Lonza
Pharma & Biotech

Solid State Characterization

- Salt screening
- Polymorph screen
- Chemical / physicochemical analyses

API Development & Supply

- Dedicated kilo-labs
- API / HPAPI (OEL 4)
- Toxicity study and first-in-human supply



Technology Selection

- Technology Review Board oversight
- Selection based on models, databases and reference maps
- Particle size reduction, spray dried dispersions (SDD), lipid based formulations (LBF)

Drug Product

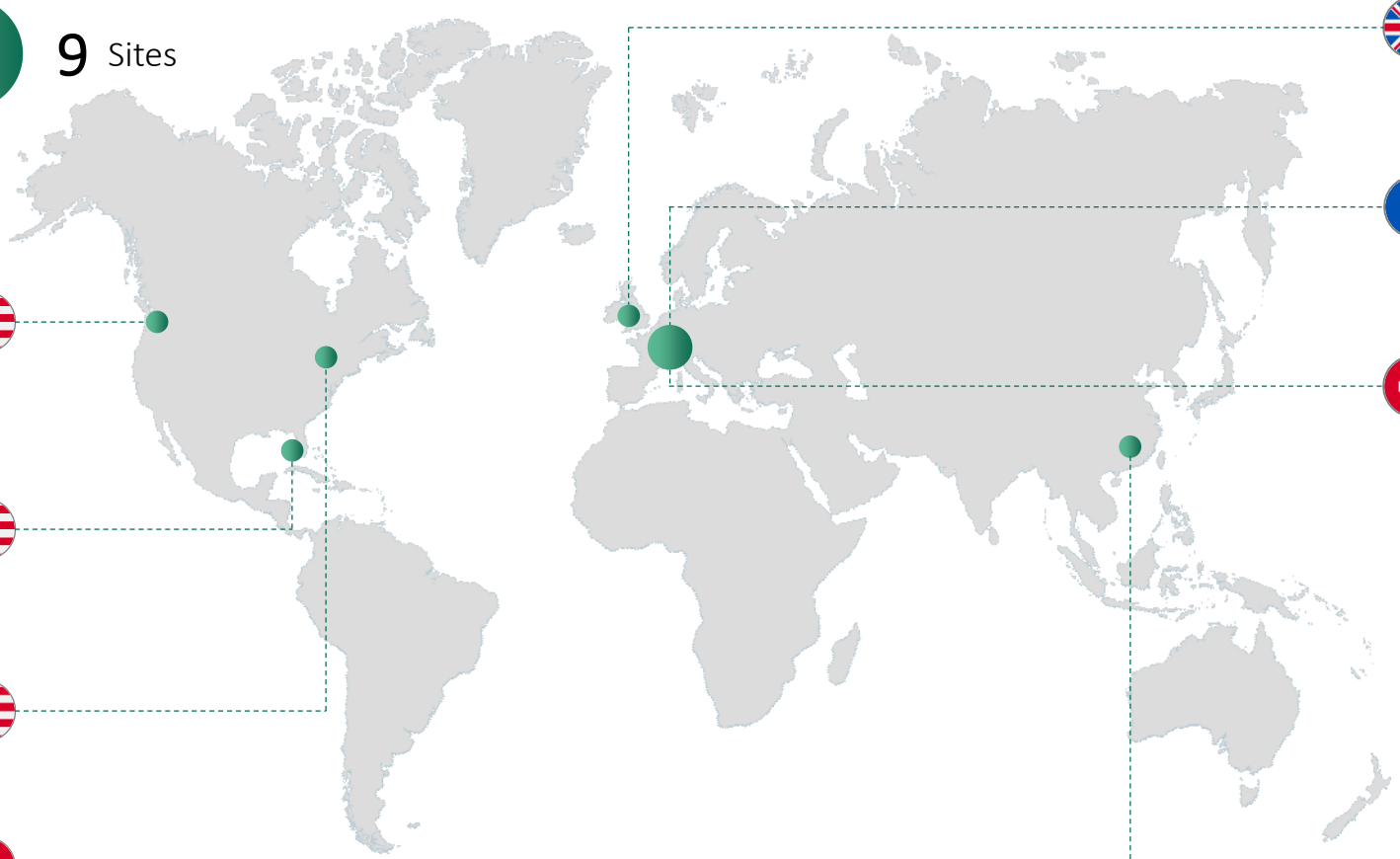
- Powder (API)-in-capsule or bottle (PIC/PIB)
- Liquid-filled hard capsules (LFHC)
- Tablets

Our global footprint in small molecules…

Lonza
Pharma & Biotech

3 Regions

9 Sites



Bend, USA
Particle engineering / solid dispersions Drug product development & **manufacturing**

Tampa, USA
Drug product development and manufacturing
Clinical supply services

Quakertown, USA
Particle engineering / jet milling

Nansha, China
API development and manufacturing

Edinburgh, UK
Drug product development & manufacturing
Lipid-based formulations / liquid filled hard capsules

Ploermel, France
Drug product development & manufacturing
Lipid-based formulations, soft gels, liquid filled hard capsules

Visp, Switzerland
Drug Substance development and manufacturing
HPAPI and ADC capabilities

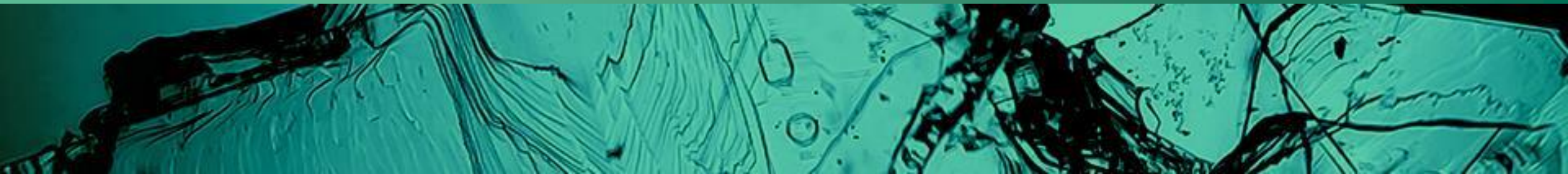
Monteggio, Switzerland
Particle engineering / jet milling

Basel, Switzerland
Drug product development & manufacturing
Parenteral / IV formulation and sterile fill/finish services

Agenda

Lonza
Pharma & Biotech

1. Crystal Form Basics
2. Why Crystal Form Matters
3. Rational Co-crystal Development
4. Q&A

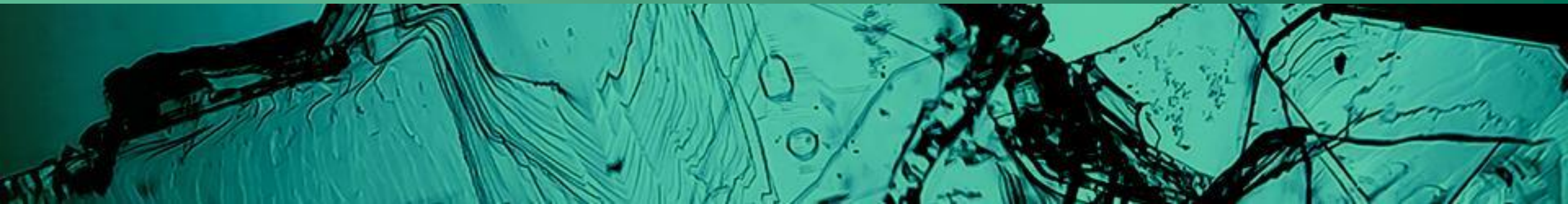


Lonza
Pharma & Biotech

SFS Overview

What are polymorphs, solvates, salts, and cocrystals?

Lonza Solid Form Services | Michael Grass and Abhijeet Sinha | March 2021



What is solid form services (SFS)?

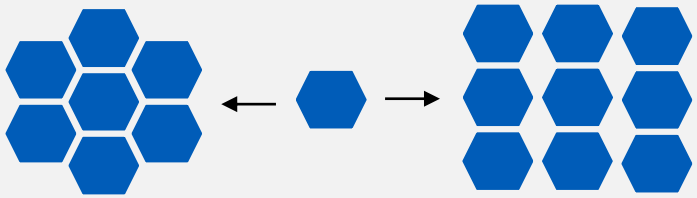
Lonza
Pharma & Biotech

The search, preparation, and characterization of solid forms in order to select a preferred solid form, design processes to isolate the preferred form, and have confidence in the stability of that form and its downstream manufacturability into drug product.

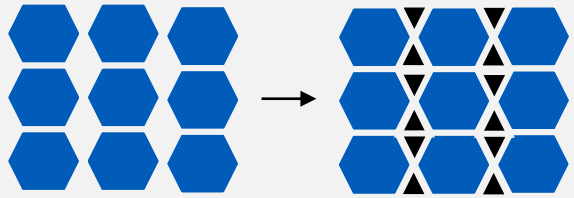
What are solid forms?

Lonza
Pharma & Biotech

Polymorphs have different molecular arrangements



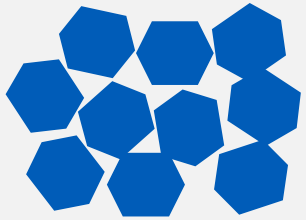
Solvates, hydrates have solvent trapped in the crystal structure



Salts are ionic crystals with 2 or more components

Cocrystals are non-ionic crystals with 2 or more components

Amorphous forms have no long range order



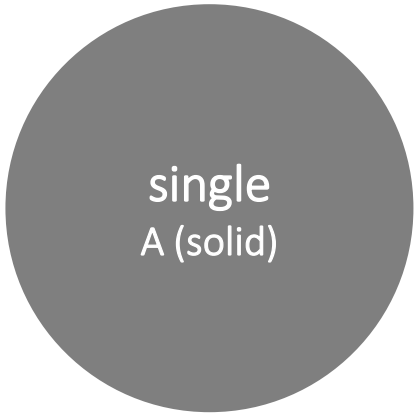
Classification of solid forms

Lonza
Pharma & Biotech

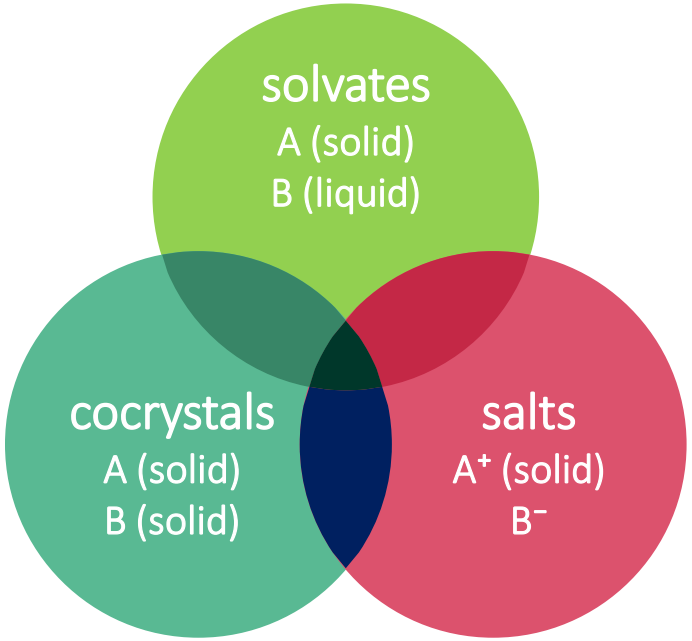
"Polymorphic forms in the context of this guidance refer to crystalline and amorphous forms as well as solvate and hydrate forms" (ICH Q6A & FDA ANDAs: Pharmaceutical Solid Polymorphism)

EU: polymorphs, solvates, hydrates, salts, and co-crystals are considered to be the same active ingredient & eligible for generic application

FDA: salts are not considered to be the same active ingredient



"Anhydrate"

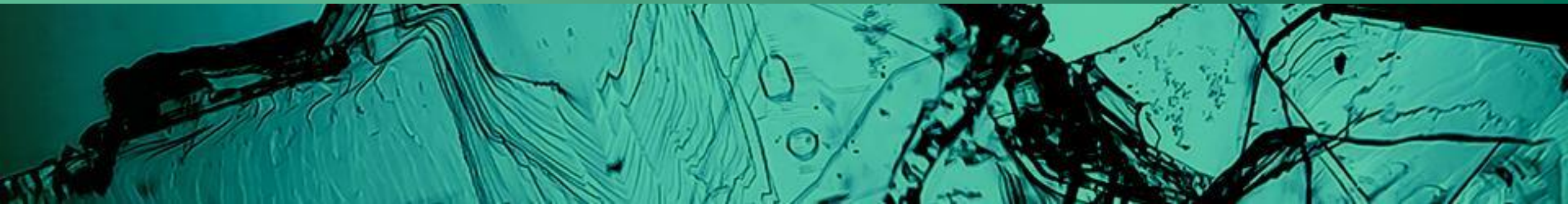


E. Grothe et al. "Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System." *Cryst. Growth Des. 16*, 2016, 3237 – 3243

Lonza
Pharma & Biotech

Why Crystal Forms Matter

Lonza Solid Form Services | Michael Grass and Abhijeet Sinha | March 2021



Solid form services (SFS) are needed to enable success

Lonza
Pharma & Biotech

- **Multiple forms are common:**
  - 89% of screened compounds exhibit multiple forms (Stahly. *Cryst. Growth Des,* **2007**, 7, 1007-1026)
- **Developing the right form first** saves time and money
- Regulatory **agencies require understanding of polymorphs, form stability, and risks to safety & efficacy**
- IP

Critical Properties Affected by Chemical and/or Polymorphic Form

Stability
- Form stability
- Chemical stability
- Hygroscopicity
- Melting & sublimation temperature

Packing
- Density
- Morphology

Purity & Appearance
- Color
- Impurity profile

Bioavailability
- Solubility
- Dissolution rate

Downstream Processing
- Applicability to drug product technologies
- Hardness
- Tensile strength
- Compactibility
- Tabletability
- Handling & filtration
- Flow & blending
- Cleavage
- Milling

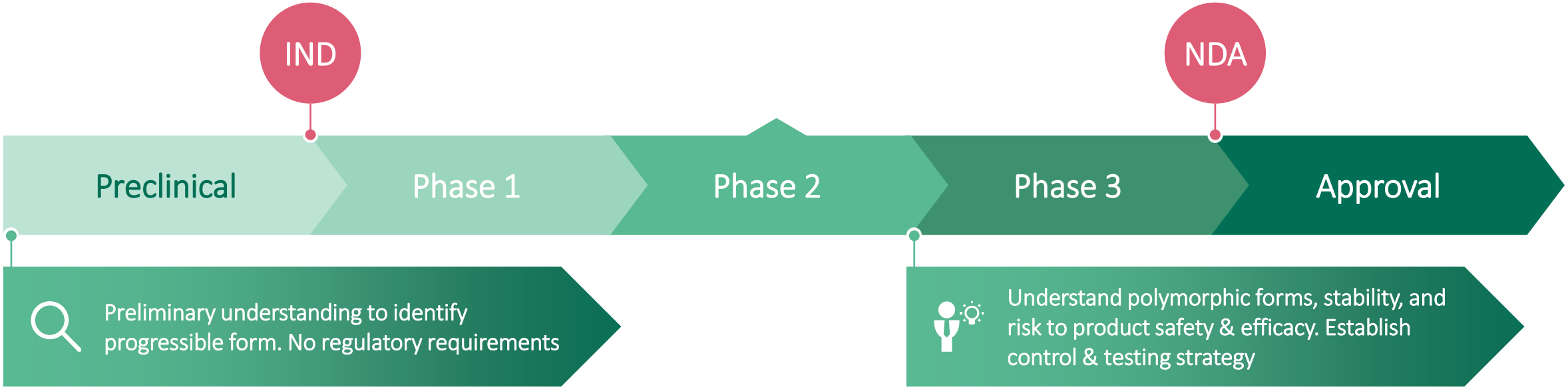
Solid form work is phase appropriate and product specific

Lonza
Pharma & Biotech

- Enable tox and FIH
- Focus on stable forms

- Risk mitigation
- Process development

- Control strategy
- Regulatory compliance
- IP protection
- Product Enhancement

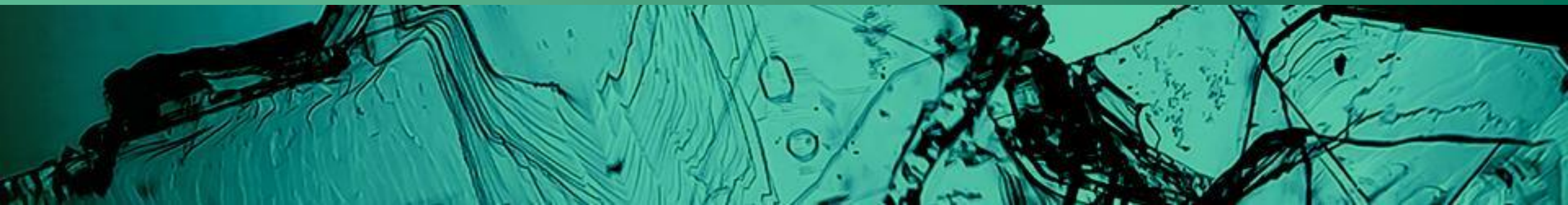


Lonza
Pharma & Biotech

Case Study 1 – Traditional Cocrystal Screen

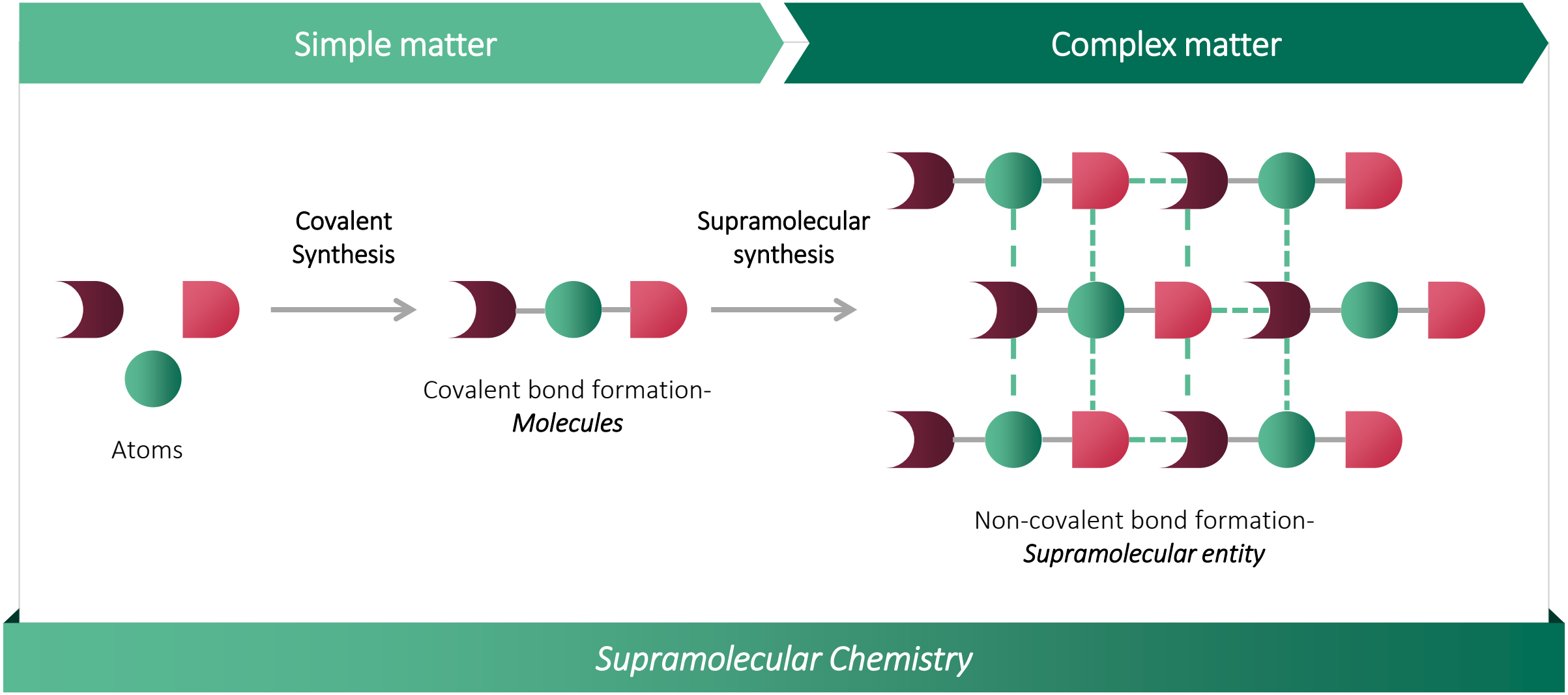
A. S. Sinha , U. B. Rao Khandavilli , E. L. O'Connor , B. J. Deadman , A. R. Maguire and S. E. Lawrence, *CrystEngComm* 2015, **17**, 4832–4841.
U. B. Rao Khandavilli, E. Skořepová, A. S. Sinha, B. R. Bhogala, N. M. Maguire, A. R. Maguire and S. E. Lawrence, *Cryst. Growth Des.* 2018, **18**, 4571–4577.

Lonza Solid Form Services | Michael Grass and Abhijeet Sinha | March 2021



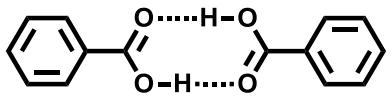
Chemistry beyond the molecule

Lonza
Pharma & Biotech

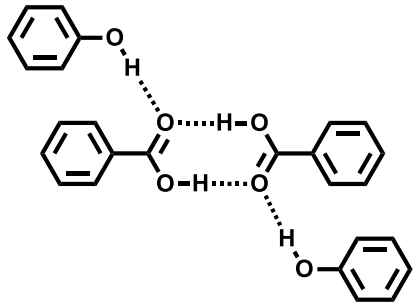


Rational cocrystal design

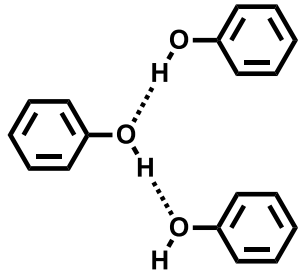
Lonza
Pharma & Biotech



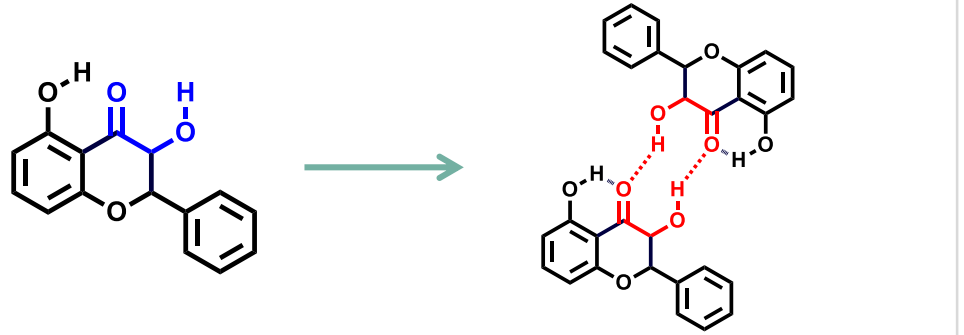
$R_2^2(8)$ dimer



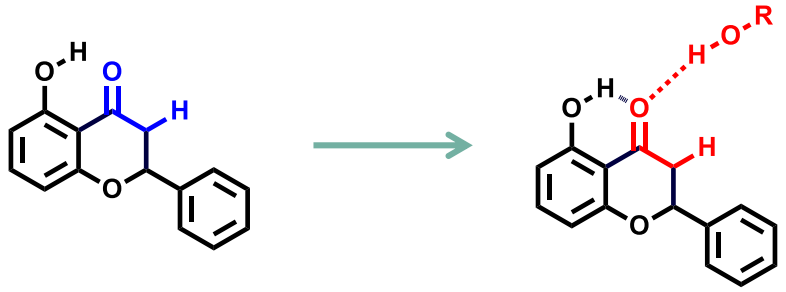
$R_2^2(8)$ dimer & D



C(2) chains



$R_2^2(10)$ dimer



D (discrete)

Robust supramolecular synthons

Why cocrystallization?

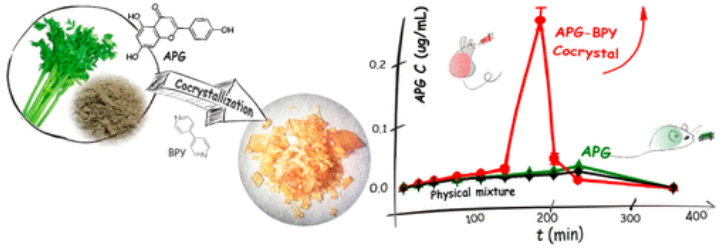
Lonza
Pharma & Biotech

Improved solubility

Cryst. Growth Des. 2018, **18**, 4571–4577

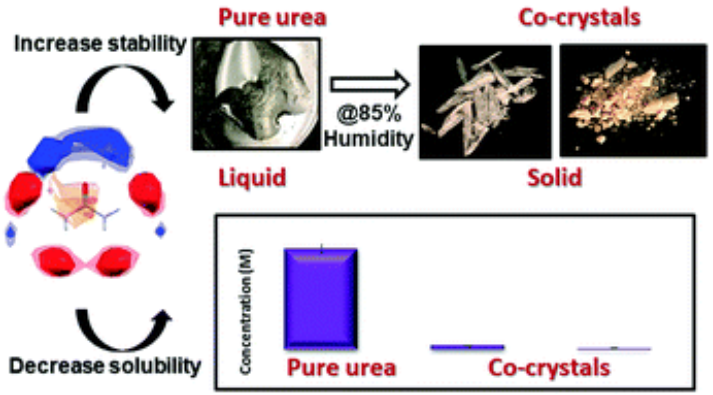
Improved bio-availability

Cryst. Growth Des. 2019, **19**, 5531–5537



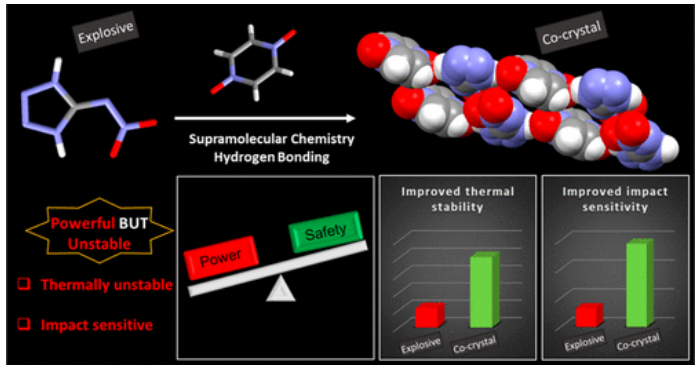
Altered solubility of agrochemicals

Chem. Commun. 2018, **54**, 4657-4660



Improved energetic performance

Cryst. Growth Des. 2020, **20**, 2432–2439



Challenges in API development

Lonza
Pharma & Biotech

Active Pharmaceutical Ingredient (API)

Processing Problems

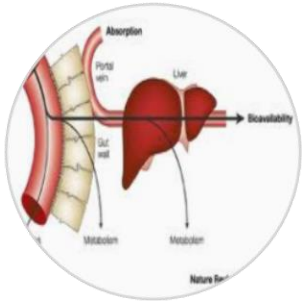
Flow

Compaction

Content Uniformity

Poor Solubility

Dissolution



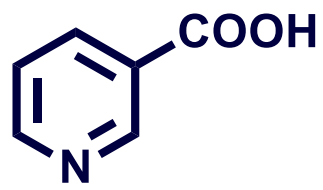
Bioavailability

https://dev.rodpub.com/images/143/084_main.jpg
http://5.imimg.com/data5/LN/LC/MY-36553/2-nitro-aniline-500x500.jpg
http://res.freestockphotos.biz/pictures/5/5483-round-biconvex-white-tablets-pv.jpg

Traditional cocrystal screening of nutraceuticals

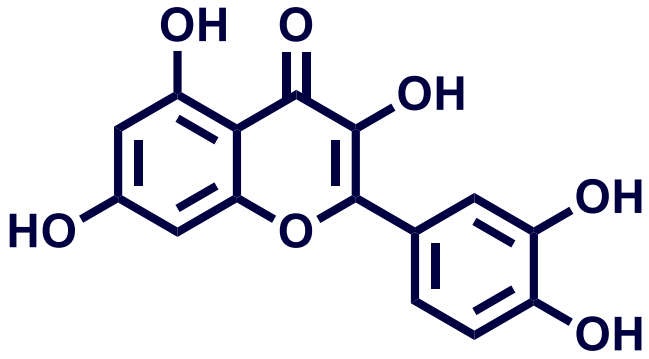
Lonza
Pharma & Biotech

a



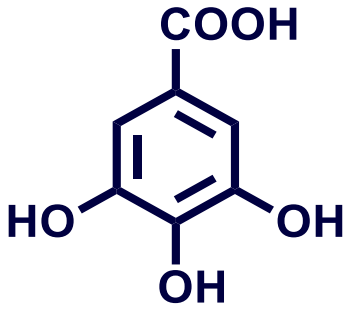
Nicotinic acid (vitamin B3)

b



Quercetin (flavonoid)

c



Gallic acid (phenolic acid)

Problem statement

- Poor solubility
- Poor stability
- Non-ionizable functional groups
- Functional group compatibility

Goals

Pharmaceutically acceptable coformers

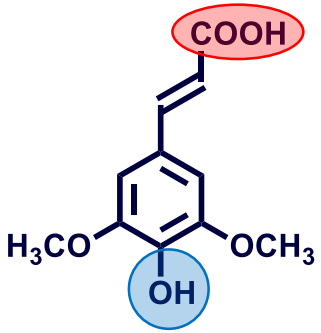
1. GRAS and EAFUS list
2. Improved physicochemical properties of nutraceuticals with health benefits

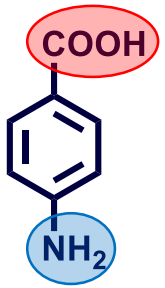
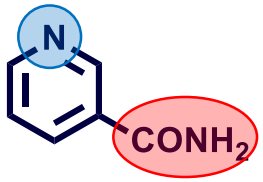
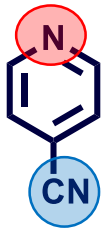
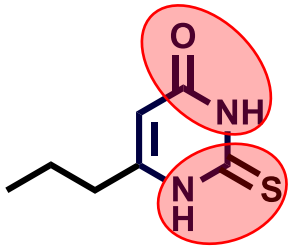
Cocrystals with relevant APIs

1. Dual drug approach
2. Anti-oxidant properties of nutraceuticals ⇨ altered physicochemical properties of APIs?

Coformers based on functional group compatibility

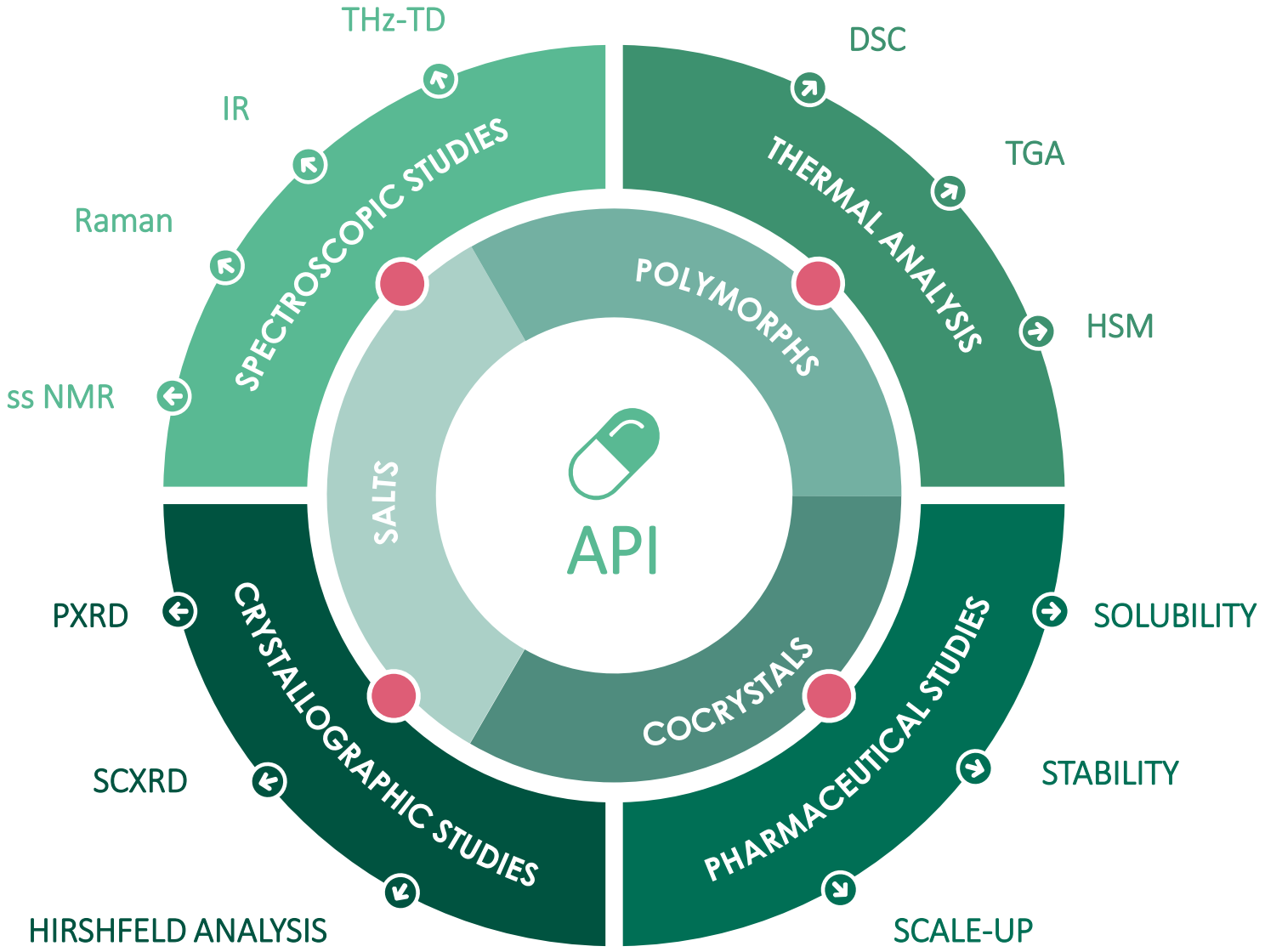
Sinapic acid



Acids	Amides	Pyridyl aromatics	APIs
			
4-Aminobenzoic acid	Nicotinamide	4-Pyridine carbonitrile	6-Propyl-2-thiouracil

Characterization and scale-up

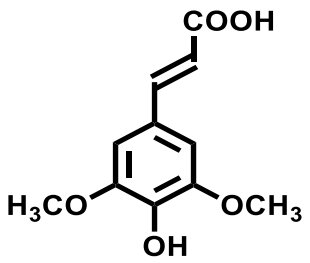
Lonza
Pharma & Biotech

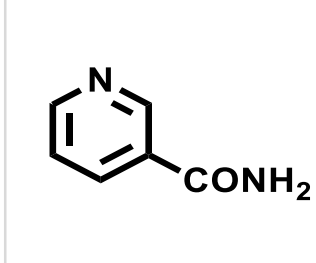


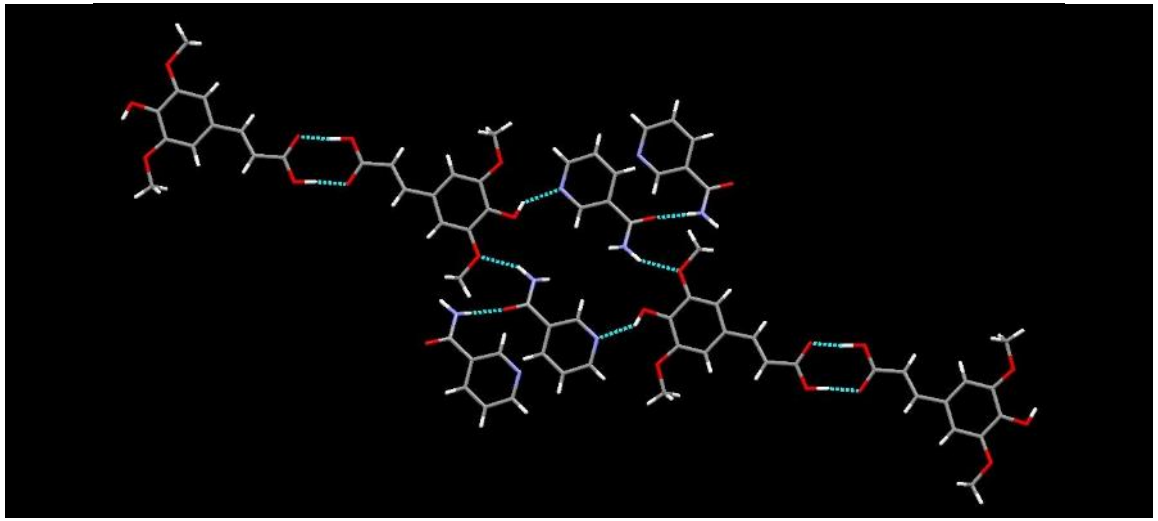
ADVANCED CHARACTERIZATION TECHNIQUES

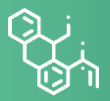
Single-crystal structures of sinapic acid

Lonza
Pharma & Biotech

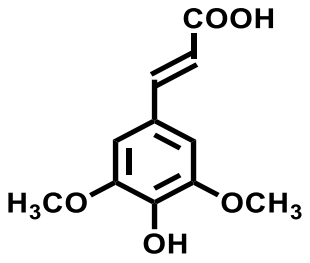


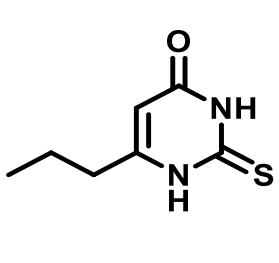


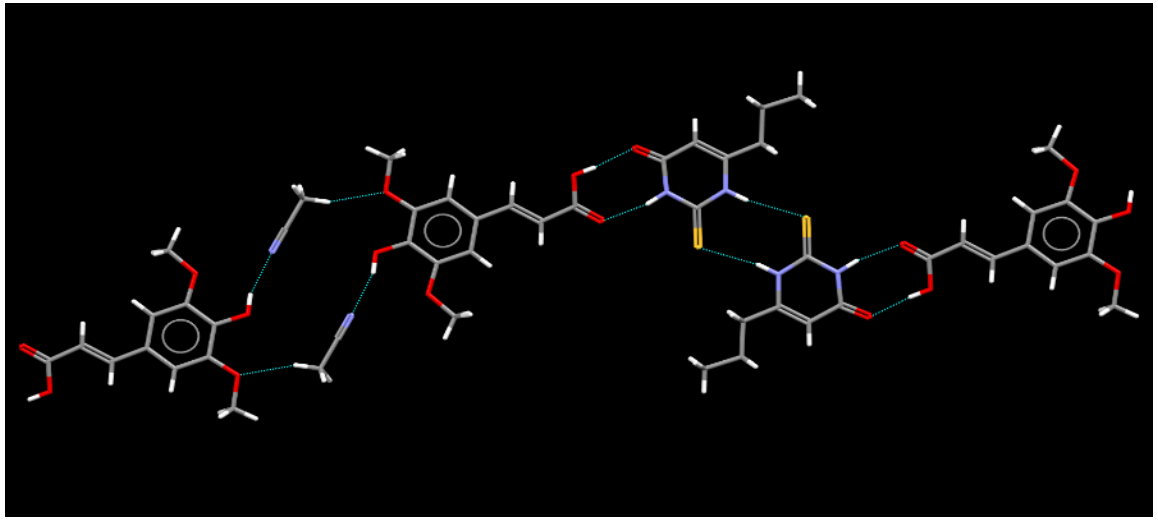


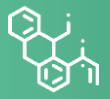


Triclinic *P*$\bar{1}$, 2; R = 5.36 %; a = 4.9109(11), b = 9.1732(18), c = 18.814(4); α = 99.563(7), β = 97.2740(10), γ = 90.531(7)





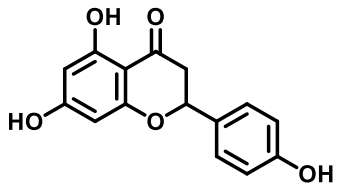


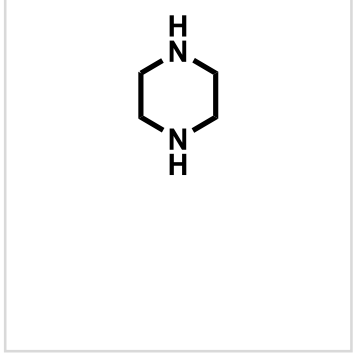


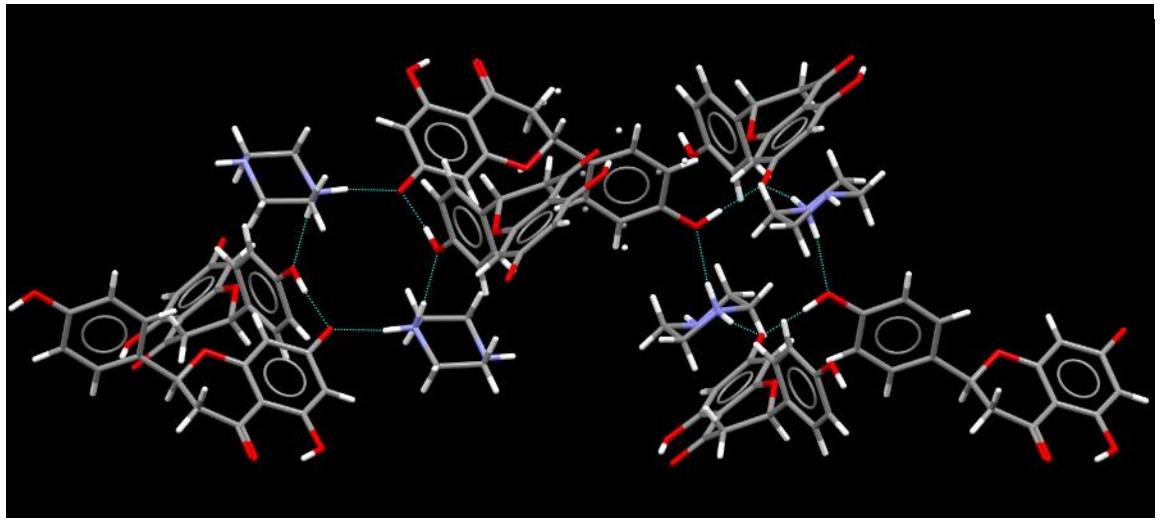
Triclinic *P*$\bar{1}$, 2; R = 3.93 %; a = 8.2922(8), b = 10.5857(10), c = 14.7818(15); α = 98.274(2), β = 94.315(2), γ = 105.620(2)

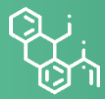
Single-crystal structures of naringenin

Lonza
Pharma & Biotech



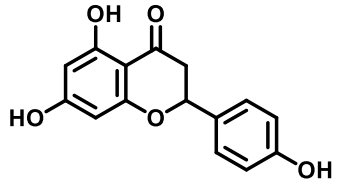


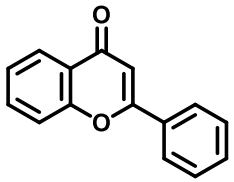


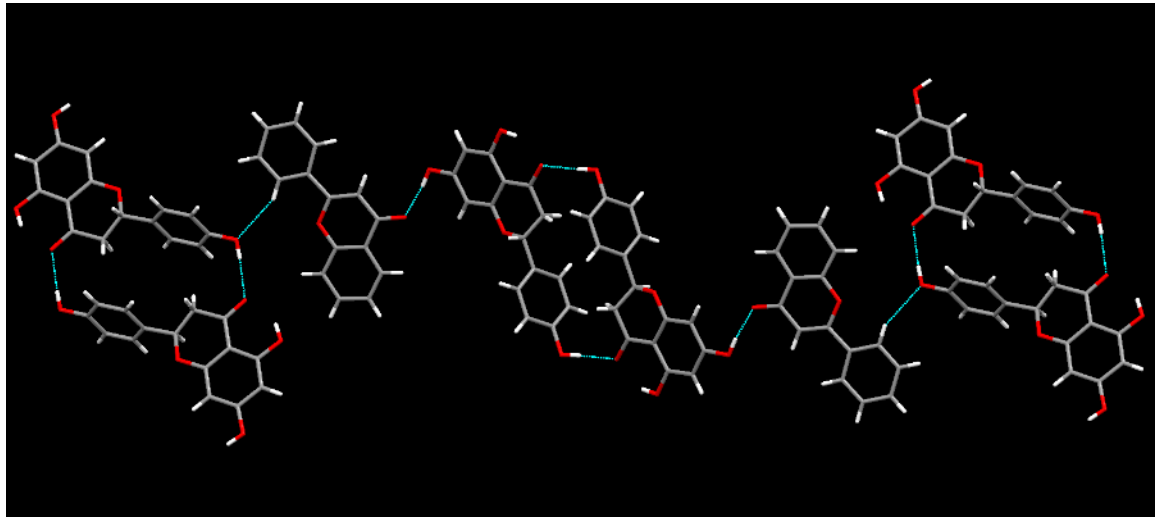


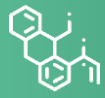
Monoclinic $P2_1/C$, 4; R = 4.46 %; a = 9.572(2), b = 18.849(4), c = 10.520(2); β = 109.072(7)

Modeled in two orientations with the final refined occupancies of 0.57:0.43/0.43:0.57.





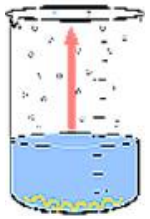




Monoclinic $P2_1/C$, 4; R = 5.55 %; a = 9.0624(2), b = 28.7469(6), c = 9.0586(2); β = 97.2740(10)

Challenges in crystallization of cocrystals

Lonza
Pharma & Biotech



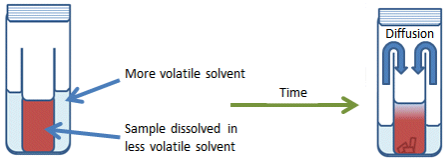
Slow evaporation

Liquid-assisted grinding (ball mill)

Solid-state grinding (ball mill)

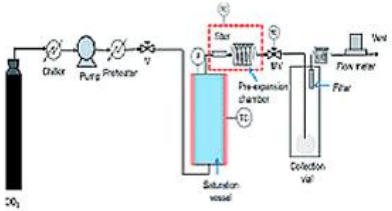
Cocrystal preparation methods

Vapor diffusion (SAS)

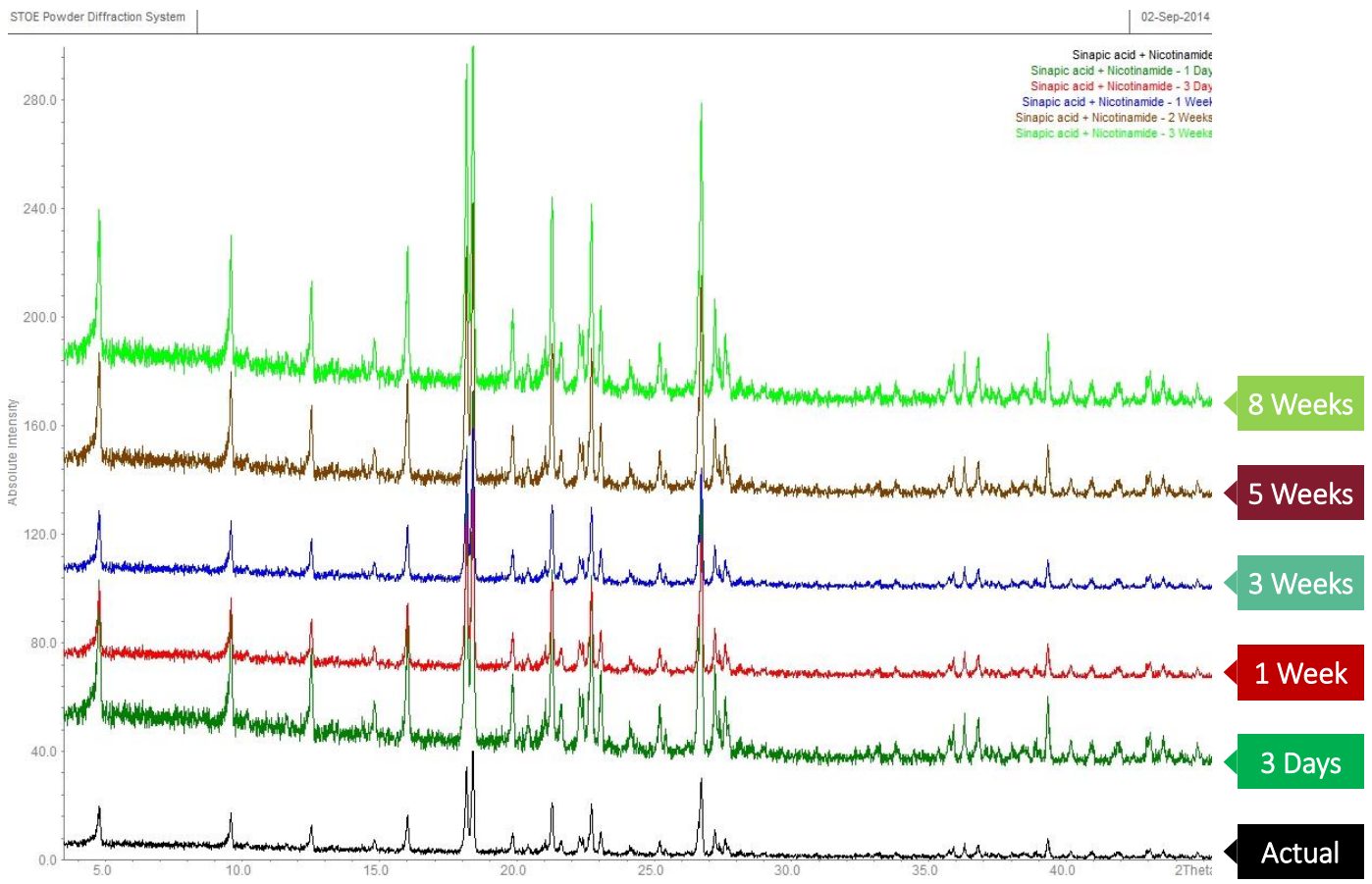


Slurry method

Supercritical fluids

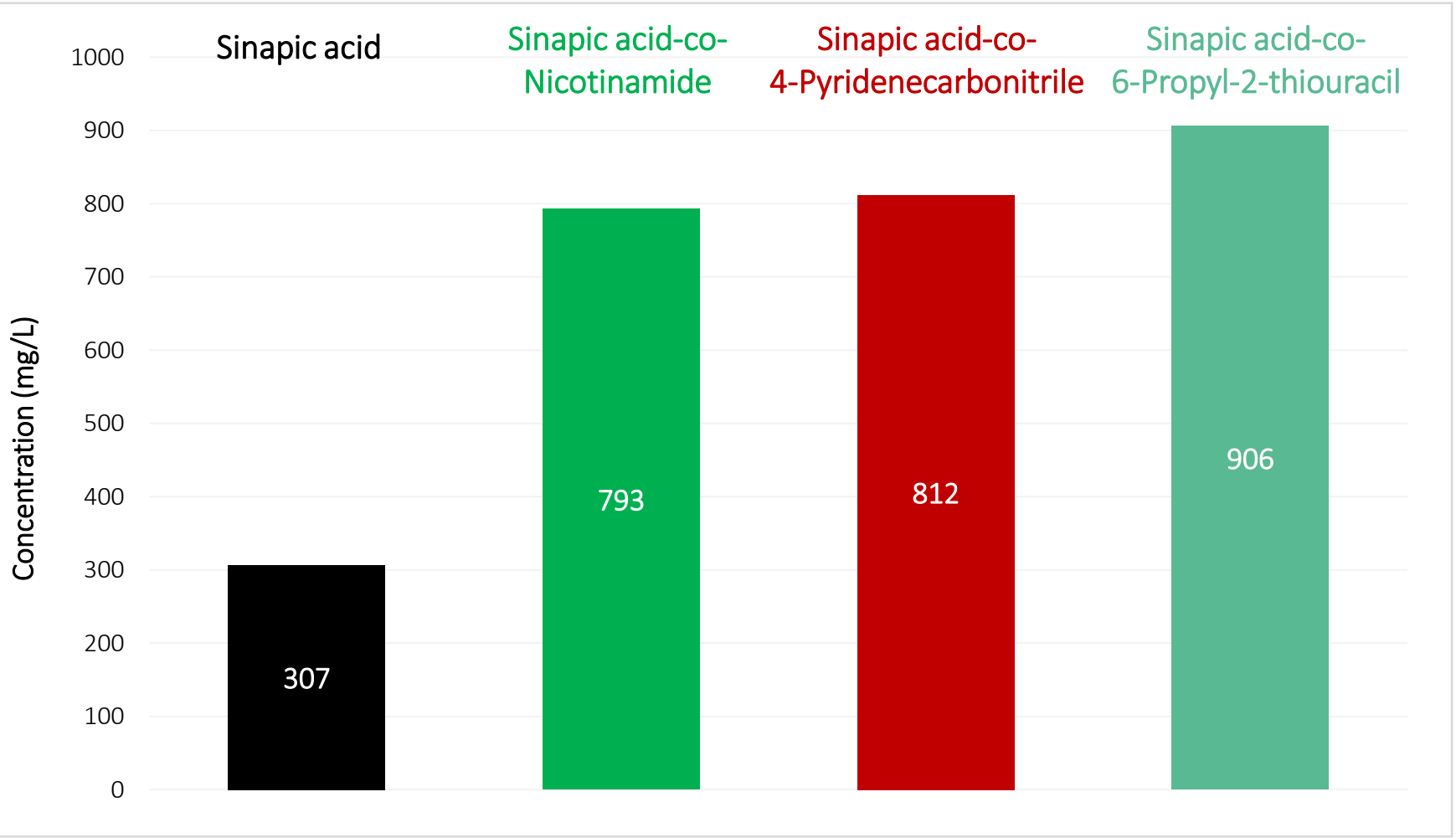


Cocrystal is physically stable



Sinapic acid + Nicotinamide (75 % RH and 40 °C)

Equilibrium aqueous solubility of cocrystals



Summary of results for case study 1

Lonza
Pharma & Biotech

Polymorph and co-crystal screening of 10 different nutraceuticals carried out.

Enhancement in physical stability of the new forms observed.

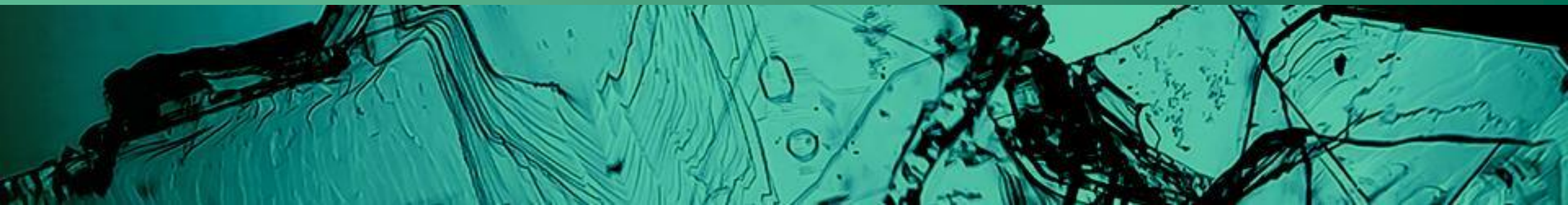
Achieved a 2-3-fold enhancement in solubility of the nutraceutical.

Lonza
Pharma & Biotech

Case Study 2 – Virtual (in-silico) Cocrystal Screen

B. Sandhu, A. McLean, A. S. Sinha, J. Desper, A. A. Sarjeant, S. Vyas, S. M. Reutzel-Edens and C. B. Aakeröy, *Cryst. Growth Des.* 2018, **18**, 466–478.

Lonza Solid Form Services | Michael Grass and Abhijeet Sinha | March 2021

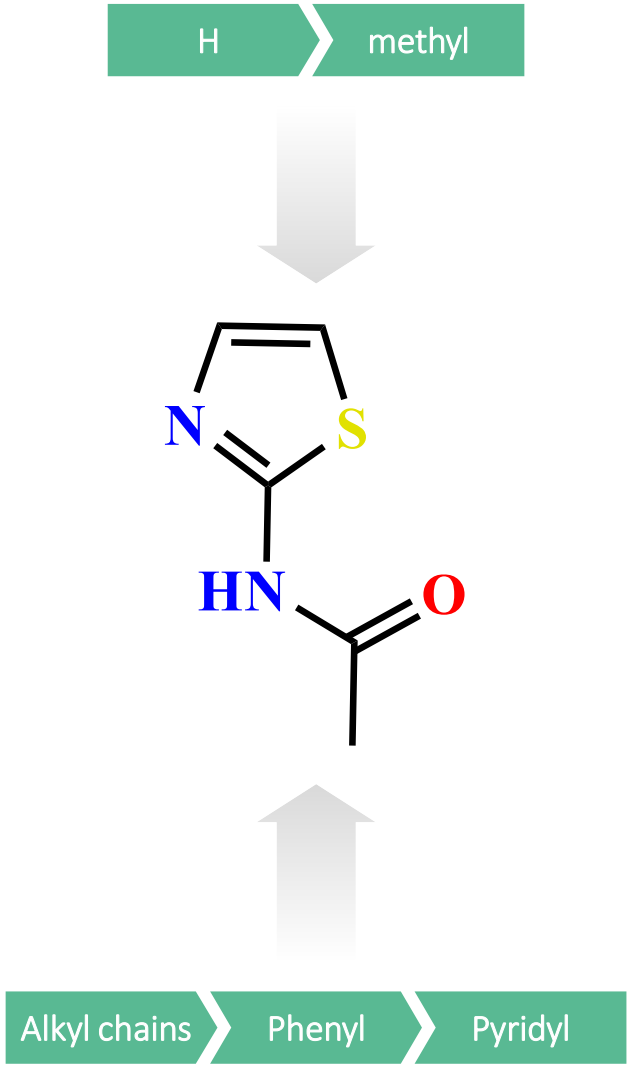


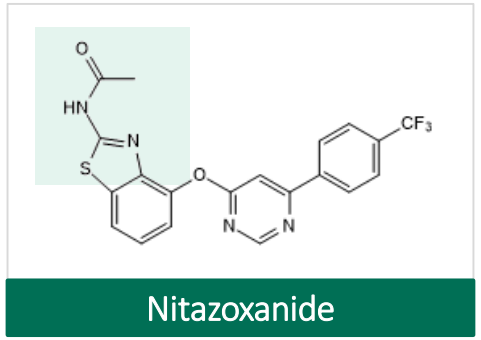
Problem statement

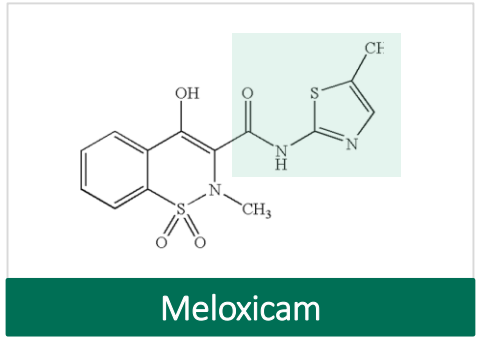
- Experimental cocrystal screening is expensive
- …and time consuming.

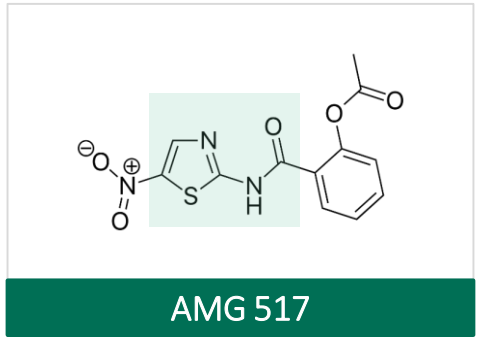
Goals

- Reduce cost and labor extensive screens via in-silico methods.
- Validate results by comparing to experimental screen.




Nitazoxanide


Meloxicam


AMG 517

Lonza
Pharma & Biotech

Experimental cocrystal screening

	Group 1						Group 2						
ACID	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T12	T12	Success rate
Suc													58%
Adi													58%
Sub													58%
Seb													50%
Dod													50%
Fum													67%
Mal													75%
Glu													58%
Pim													50%
Aze													42%
3-HydroxyBA													100%
4-HydroxyBA													83%
3-AminoBA													92%
4-AminoBA													67%
3-NitroBA													100%
4-NitroBA													50%
BA													67%
4-IodoBA													8%
4-BromoBA													16%
PentaFBA													100%
Positive outcomes	7	8	4	5	6	11	19	18	19	18	18	18	**151/240**
Success rate	35%	40%	20%	25%	30%	55%	95%	90%	95%	90%	90%	90%	**63%**

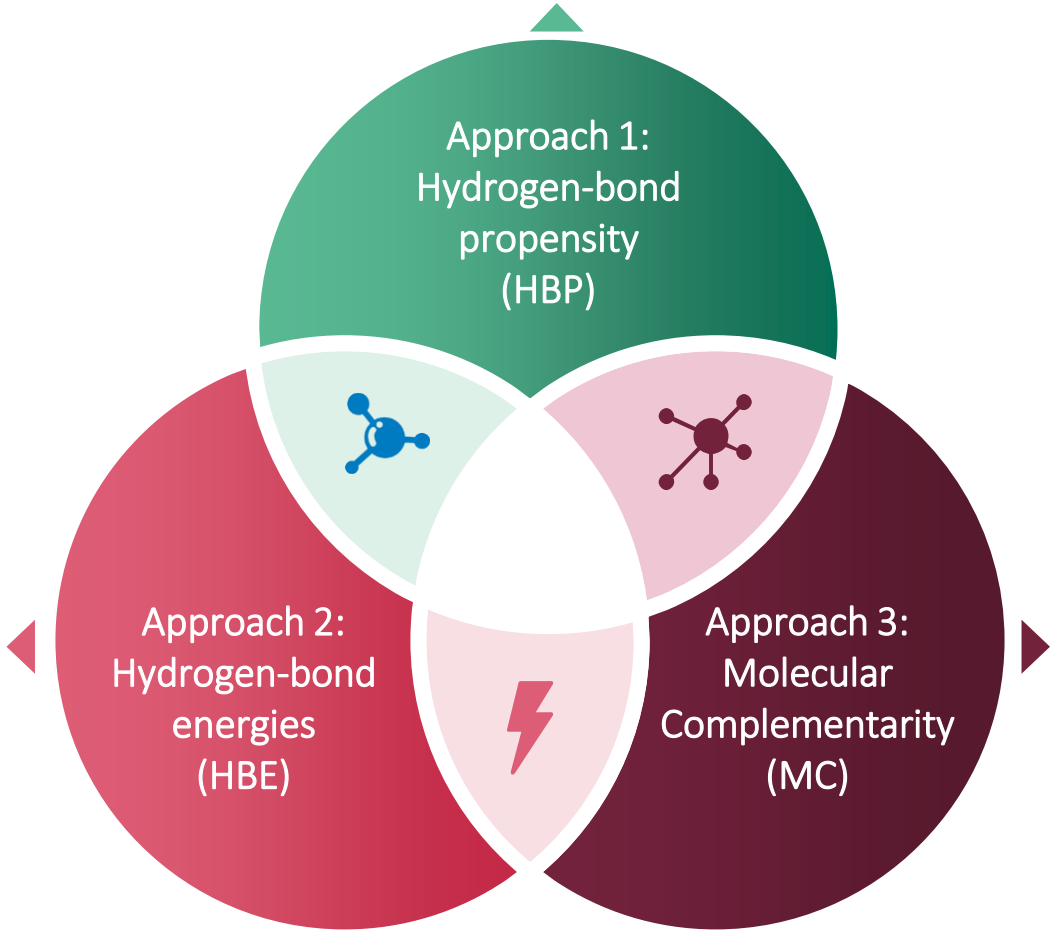
Red = No Green = Yes

Methods to predict cocrystallization outcome

Lonza
Pharma & Biotech

$$\text{HBP } score = \left(\begin{matrix}\textbf{Propensity of the best}\\ \textbf{heteromeric interaction}\end{matrix}\right) - \left(\begin{matrix}\textbf{Propensity of the best}\\ \textbf{homomeric interaction}\end{matrix}\right)$$

0.00 as cut off



$$\text{HBE } \textbf{score} = \left(\begin{matrix}\textbf{Energy of the best}\\ \textbf{heteromeric interaction}\end{matrix}\right) - \left(\begin{matrix}\textbf{Energy of the best}\\ \textbf{homomeric interaction}\end{matrix}\right)$$

0.00 as cut off

10 by 10 conformations
Hit rate: >50% (positive cocrystal)

Lonza
Pharma & Biotech

Approach 1: Can we use HBP to predict cocrystallization?

$$\text{HBP } score = \left(\begin{matrix}\textbf{Propensity of the best}\\ \textbf{heteromeric interaction}\end{matrix}\right) - \left(\begin{matrix}\textbf{Propensity of the best}\\ \textbf{homomeric interaction}\end{matrix}\right)$$

0.00 as cut off

		Predicted outcome	
		Cocrystal	No cocrystal
Experiment	Cocrystal	True positive	False Negative
	No cocrystal	False Positive	True Negative

Group 1

MC_{cutoff}:>0.00		Predicted outcome	
		Cocrystal	No cocrystal
Experiment	Cocrystal	49	31
	No cocrystal	17	63

112/ 160 = 70%

Group 2

MC_{cutoff}: >0.00		Predicted outcome	
		Cocrystal	No cocrystal
Experiment	Cocrystal	48	25
	No cocrystal	0	7

55/ 80 = 68%

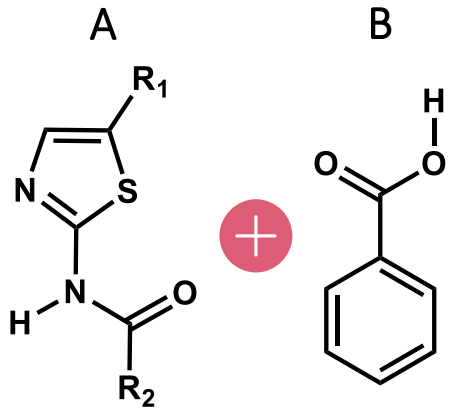
Overall success rate = 69%

Approach 2: Can we use HBE to predict cocrystallization?

$$HBE\ score = \left(\begin{matrix}\textbf{Energy of the best}\\ \textbf{heteromeric interaction}\end{matrix}\right) - \left(\begin{matrix}\textbf{Energy of the best}\\ \textbf{homomeric interaction}\end{matrix}\right)$$

0.00 as cut off

E= best Donor ✖ best acceptor
E= α ✖ β



AA | AB | BA | BB

Heteromeric

Homomeric

Group 1 → Success rate 50%

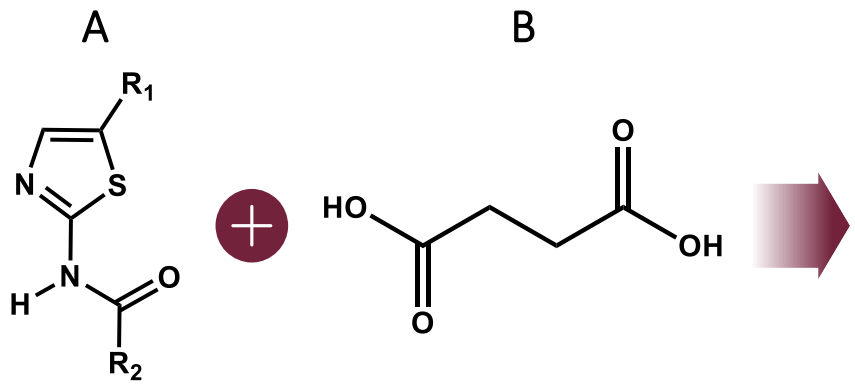
Group 2 → Success rate 84%

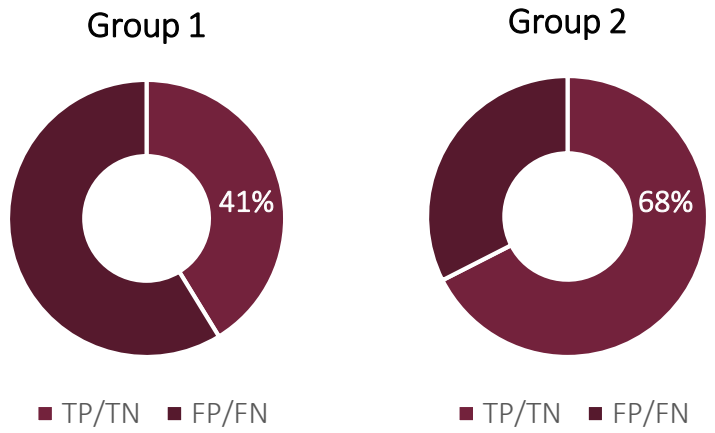
Overall success rate = 62%

Lonza
Pharma & Biotech

Approach 3: Can we use MC to predict co-crystallization?

MC= Molecular complementarity

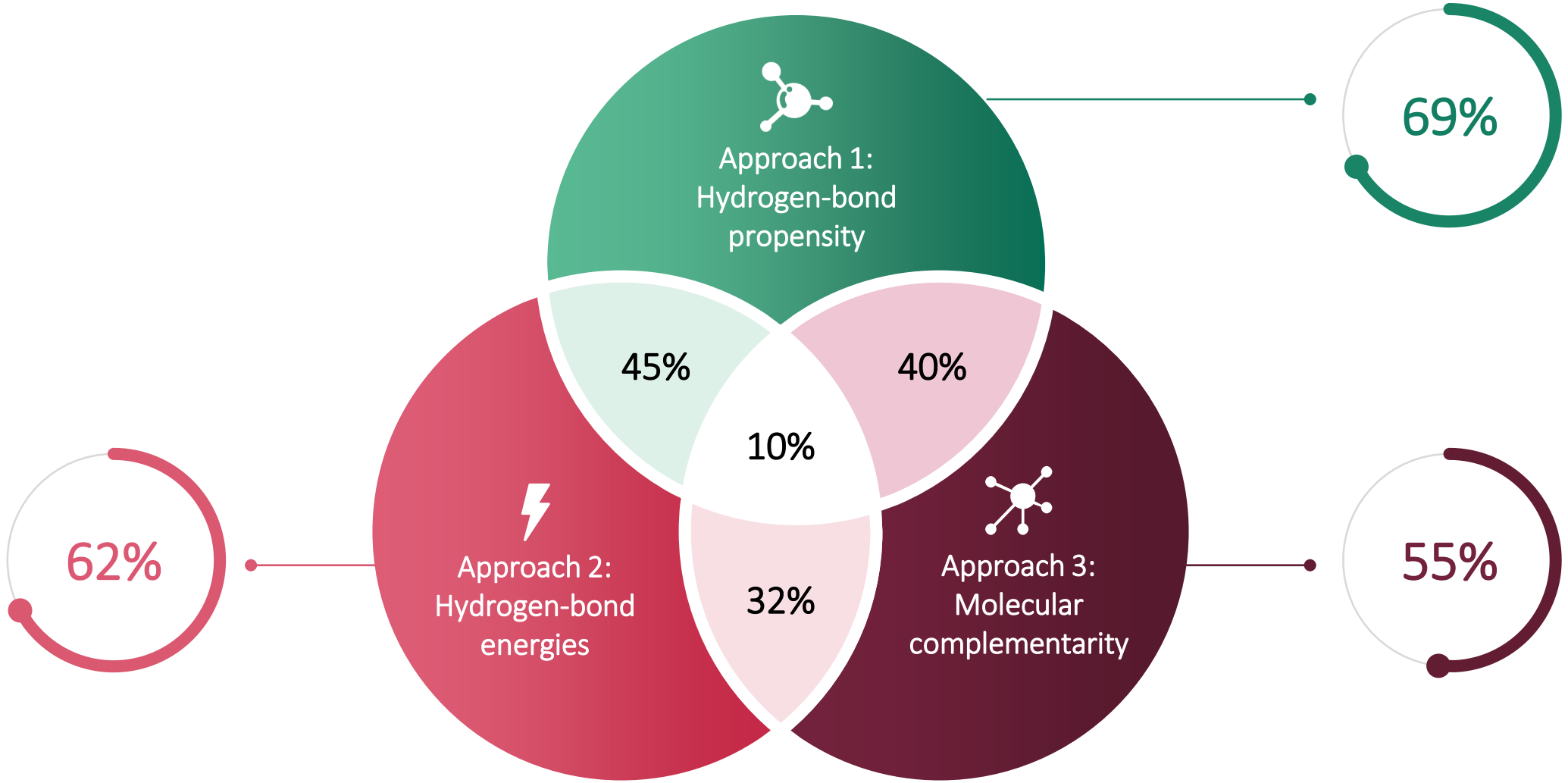




Overall success rate= 55%

T1			
Co-former	Hit rate %	Experimental	Match?
SuccinicAcid	90	✓	
AdipicAcid	100	×	
SubericAcid	100	×	
SebacicAcid	100	×	
DodecaendioicAcid	90	×	
FumaricAcid	100	×	
MalonicAcid	22	×	
GlutaricAcid	100	×	
PimelicAcid	100	×	
AzelaicAcid	100	×	
3-HydroxyBA	100	✓	
4HydroxyBA	100	✓	
3AminoBA	100	✓	
4AminoBA	100	✓	
3NitroBA	88	✓	
4NitroBA	100	✓	
BA	100	×	
4BromoBA	100	×	
4IodoBA	100	×	
PentaFBA	100	✓	

Summary of results for case study 2



Conclusions

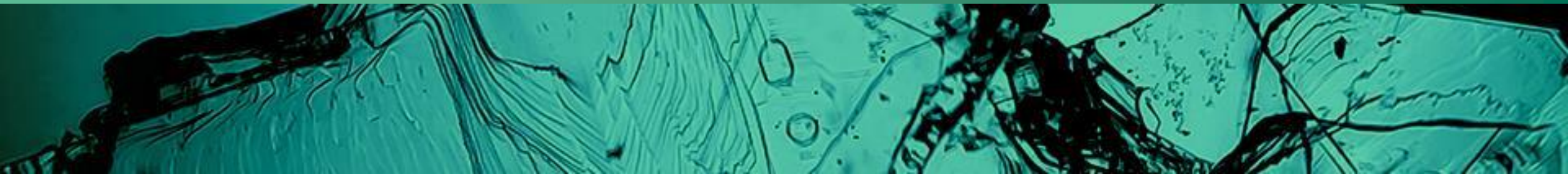
Lonza
Pharma & Biotech

- Solid form screening and selection is a key aspect of drug development and clinical readiness.
- Identifying robust supramolecular synthons and understanding their hierarchy within different intermolecular interactions is key to rational cocrystal design.
- Cocrystallization of 10 nutraceuticals resulted in multiple new solid-state forms with GRAS and EAFUS acceptable coformers.
- A 2-3 fold increase in solubility of the nutraceutical was observed in the cocrystals.
- Virtual cocrystal screening is important for saving time and cutting costs associated with traditional screens.
- For the examined pharmacophore, hydrogen bond propensity (HBP) method had the highest success rate for predicting cocrystals.

Solid Form Screening

Webinar - Solid Form Screening and Rational Cocrystal Design

Lonza
Pharma & Biotech



the next relationship…

Working in partnership.

pharma.lonza.com

small.molecules@lonza.com