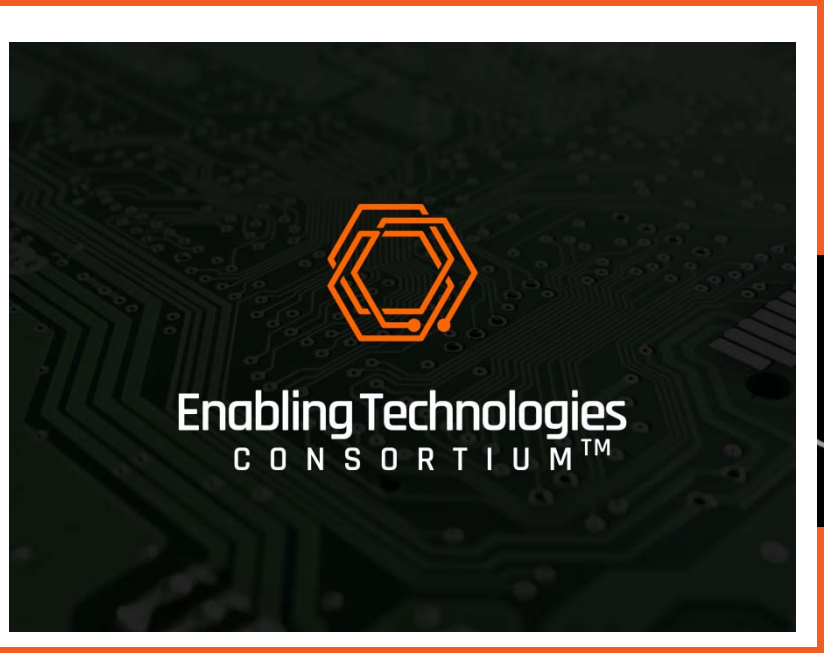


Shedding a Light on Solubility Measurement and Prediction
Solubility Sub Team's Story to Date

Outline

- Why is organic solubility important?
- Organisation of the group
  - HTE working group
  - Prediction working group
- Experimental results
- Conclusion
- Questions

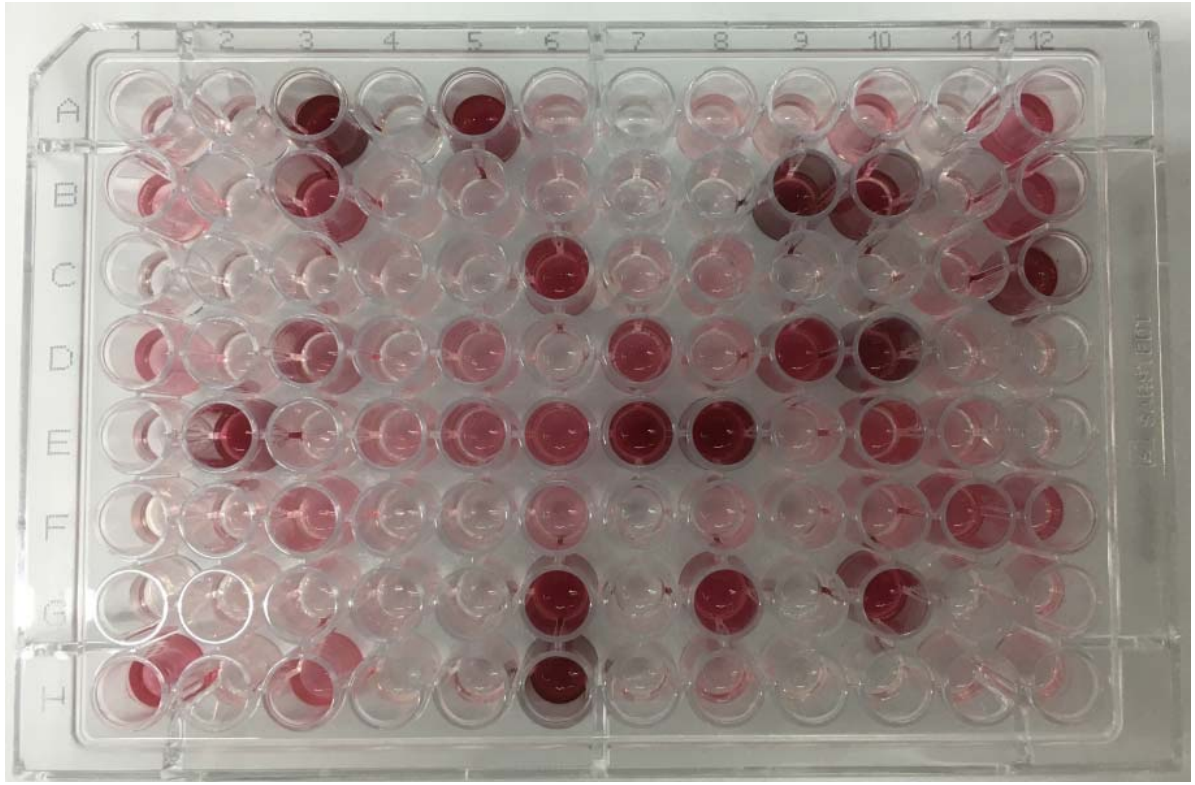
Why is organic solubility important?

- Organic synthesis requires organic molecules and organic solvents at different temperatures
  - Different to biological testing (APIs, water based and body temperature)
- Most of the ETC members use solubility to facilitate process development (scale up) of chemical reactions
  - Solubility *precipitates* into everything we do

Why is organic solubility important?

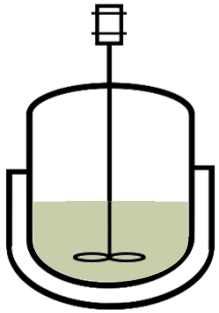
Solubility data contributes to
Improving experimental efficiency
Developing processes faster
Reducing risks and costs
for the development and
manufacture of new drugs

Why is organic solubility important?

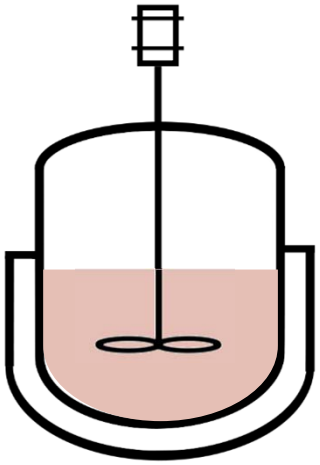


High Throughput Experimental (HTE)
Planning & Experimentation

Why is organic solubility important?

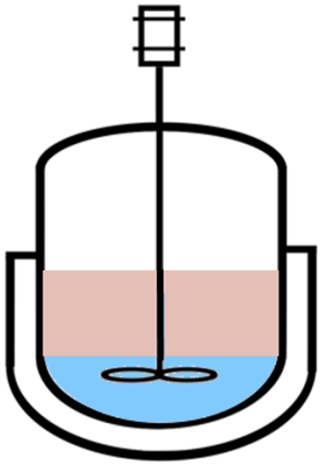


Reactant/Reagent makeup



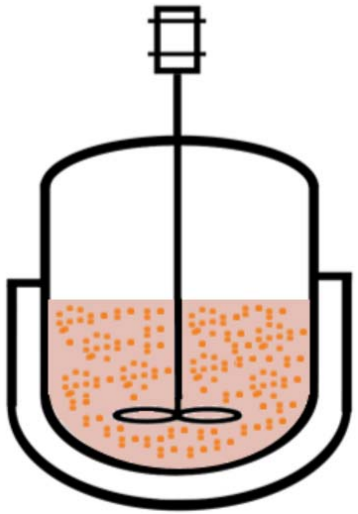
Reaction solubility
- Starting Material(s)
- Product
- Impurities
- Prevent uncontrolled reaction

If it's not in solution, it's not reacting (generally!)



Workup
- Extractions
- Impurity rejection

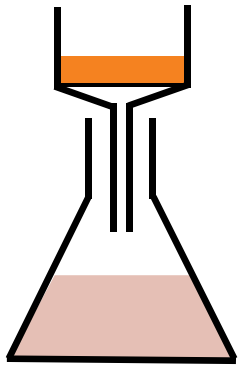
What is going where, when



Isolation
- Direct drop
  - Temp
  - Concentration
- Anti-solvent

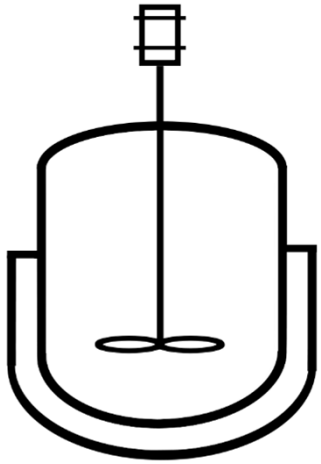
Isolate the same yield, form and purity each time

Why is organic solubility important?



Filter washing
- Remove difficult solvents
- Last chance to remove impurities (organic/inorganic)

Don’t wash away your yield!



Cleaning solvent
- Next batch
- Next process

Avoid batch failure / delays in processing

ETC solubility working parties

HTE

Modelling & Prediction

However much capacity you have to measure solubility it will ***never be enough***

1000's of compounds
100's of solvents
10,000's of binary mixtures
Finite, but highly divisible temperature range

HTE isn't VVVVVVVUHTE

Prediction to fill in the gaps

ETC solubility working parties

Aim:

- To define and develop with a partner the ‘Next Generation Automated Solubility Platform’ for cheap, easy to use measurement of organic solubility

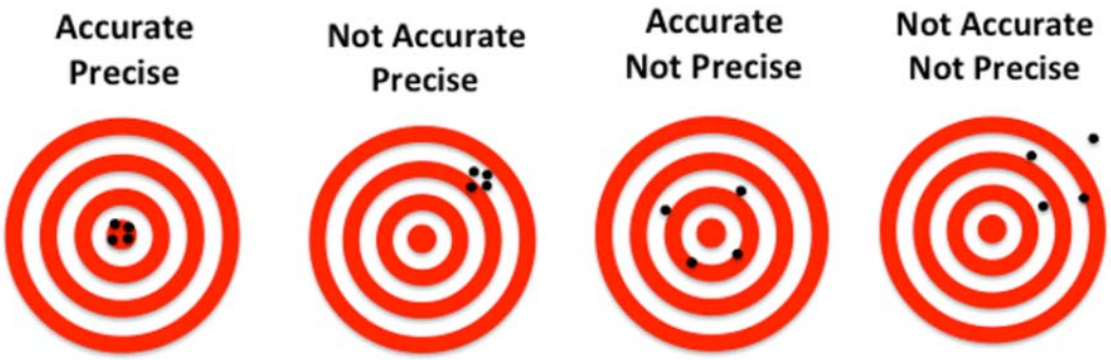
Complemented with

- Understand the error in predictions from different models.
- Find their relative strengths and weaknesses.
- Use this understanding to develop best practices.
- Publish findings in the open literature.

Challenges in measurement

- It needs to be ‘correct’
  - Once written down, people assume it to be true!

- Almost all operations in measurement can affect accuracy and precision

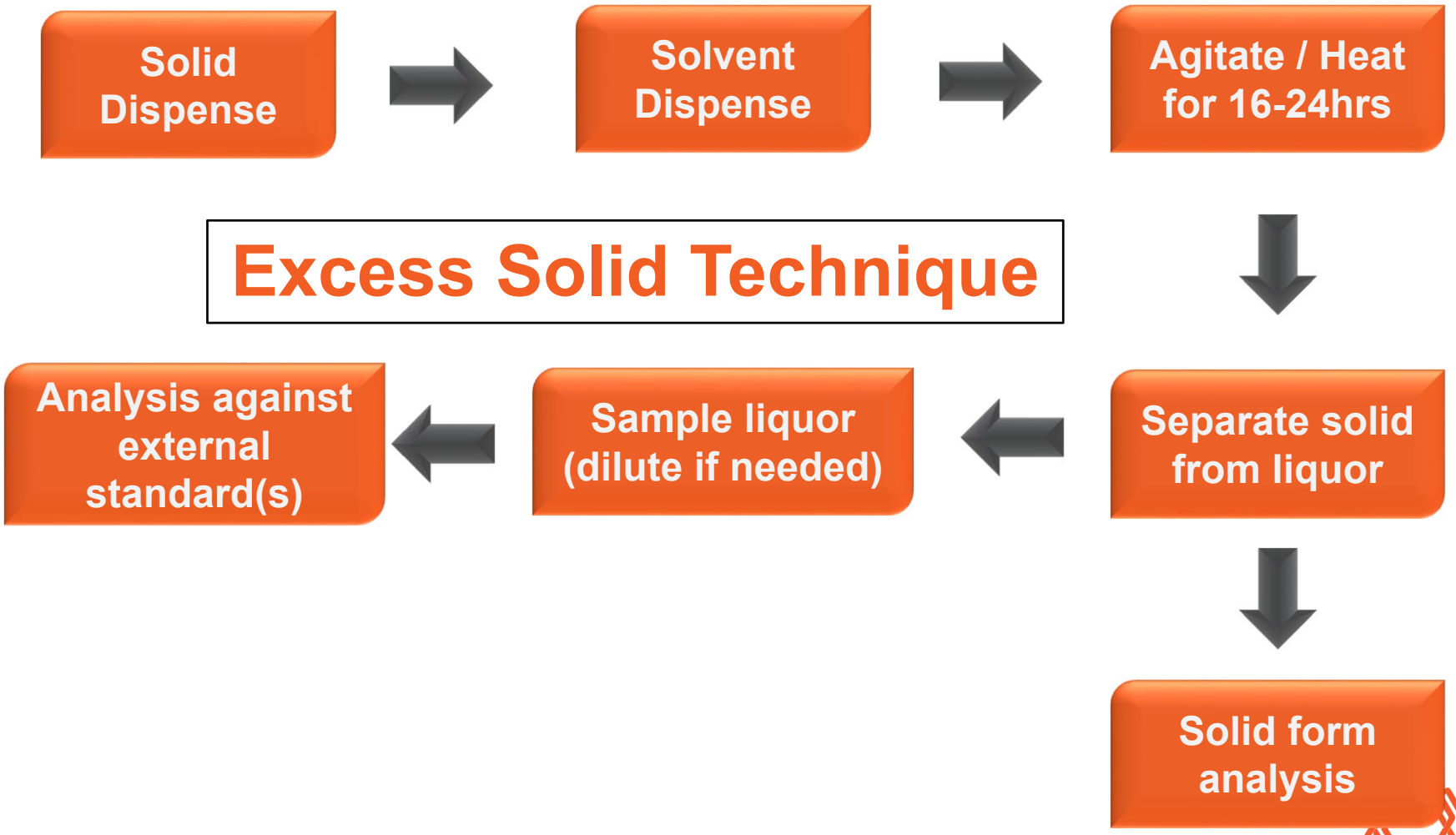


Challenges in measurement

- Solubilities can vary from 0.1mg/mL to >500mg/mL for one solute, depending on solvent and temperature
- Pipettes / needles are calibrated for water at STP
- Ideally measure solubility of thermodynamic stable material
  - Leave to equilibrate over many hours
  - Organic solvents like to evaporate!
- Polymorph analysis is key to knowing what ‘solubility’ you have measured.

HTE screening across the companies

- Reviewed our current methodologies
- Different equipment, same principles



Current practice vs. RFI statement

Compatible Materials of Construction
Acidic / basic / corrosive solutions

Use of glass or glass lined PP. Teflon caps. Disposable tips. SS needles.

Run on >24 vials at once
(Optional – 2mg to 5mg material per well)

Run on 24 to 96 well plates
(20mg to 50mg material per well)

Excess Solid Technique

Ability to measure from 0.1 mg/mL to 250 mg/mL

0.1 mg/mL to >250 mg/mL

Known accuracy and precision across all measurements

See results later

Current practice vs. RFI statement

Solid Dispense

Integrate with solid handler
(learn from ETC group)

Use of Unchained CM3, Mettler Toledo Quantos and Chemspeed Swing as well as manual

Current practice vs. RFI statement

Solvent Dispense

Ability to tune liquid dispensing to maintain accuracy and precision of dispense **for each solvent**

- For single solvents, less critical
- Making up binary mixtures does require accuracy
- Mixture of ADT, PDT, Robot

Current practice vs. RFI statement

Agitate / Heat for 16-24hrs

- Mixing technology
- Temperature -20°C to 70°C (optional 120°C)
- Excellent solvent retention, important for binary mixtures

- Vortexers, tumble stirring and rotary stirring all used.
- Mixture of temps able to reach
- Mixture of vials that allow good solvent retention.

[for single solvents, as long as there is enough solvent to sample then you can accept some evaporation]

Current practice vs. RFI statement

Separate solid from liquor

- Avoid if alternative technique available
- Maintain temperature, minimise evaporation
- (Optional – Allow multiple samples from same source)

- Centrifuge
- Filter vials
- Filter plates
- Vial inserts

Current practice vs. RFI statement

Sample liquor (dilute if needed)

- Need the ability to sample supernatant with automated liquid handler
- Avoid dilution if possible (direct analysis)
- Ability to tune liquid dispensing for each solvent to maintain accuracy and precision of dispense (gravimetric)

- Some use automated liquid sampling (deck robot or HPLC autoinjector)
- Some use ADT and PDT
- Some calibrate the systems for different solvents and temperatures.
- Most go through single or double dilution

Current practice vs. RFI statement

Analysis against external standard(s)

- Not defined what technique
- System needs to be compatible with technology if external to main kit (i.e. HPLC vials for an HPLC auto sampler)

- All use (U)HPLC as analytical technique
- Number of standards and prep differs between members

Current practice vs. RFI statement

Solid form analysis

- System has to allow access to solid at the end of run for form analysis
- (Optional add on capability for form analysis)

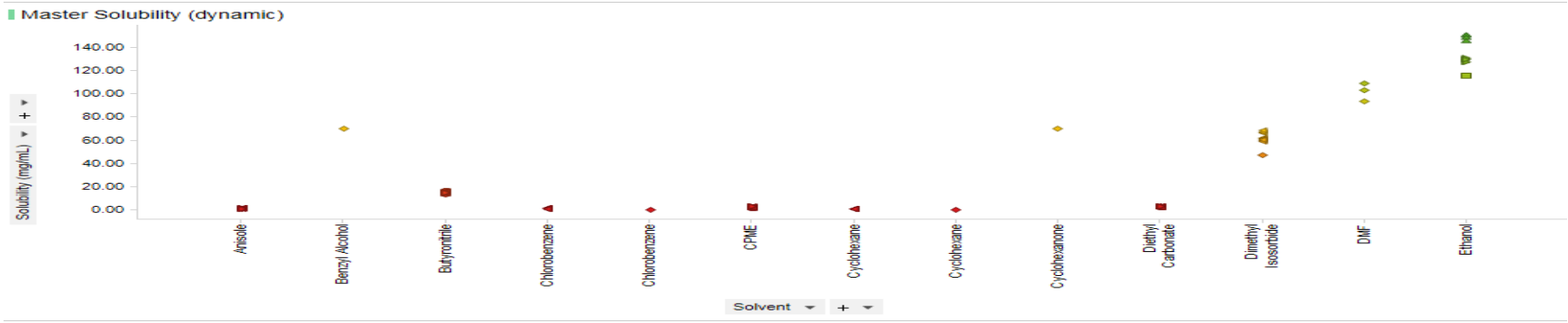
- Some members get form analysis
  - XRPD is used by these members

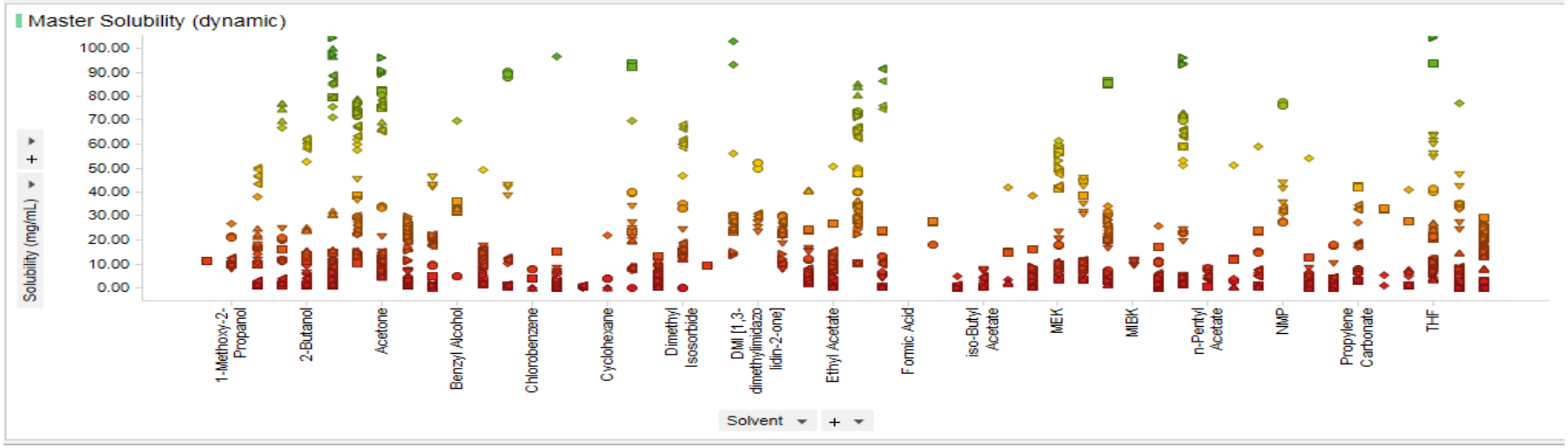
Full RFI can be found at:

http://www.etconsortium.org/solubility-platform

Modelling and Prediction

Filling in the gaps and expanding on empirical measurements





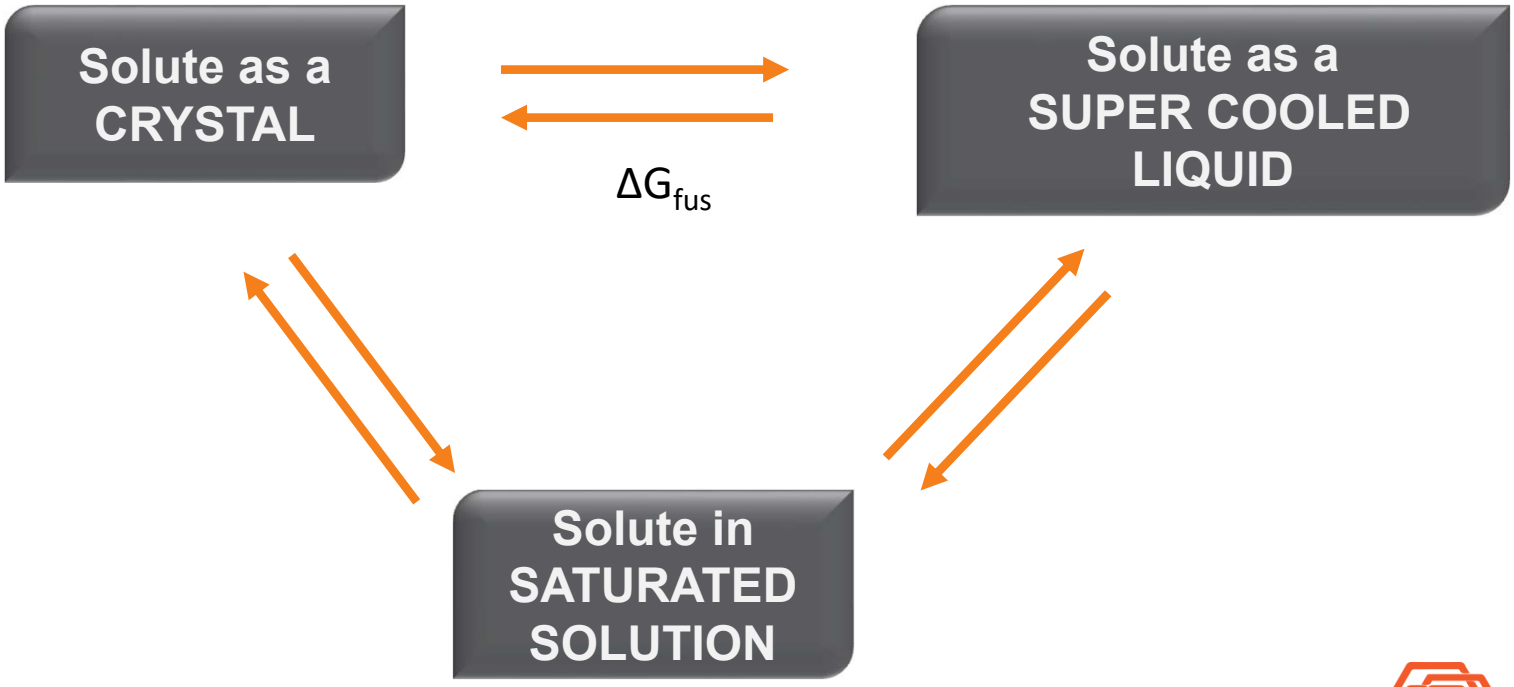
Modelling and Prediction

ΔG fusion

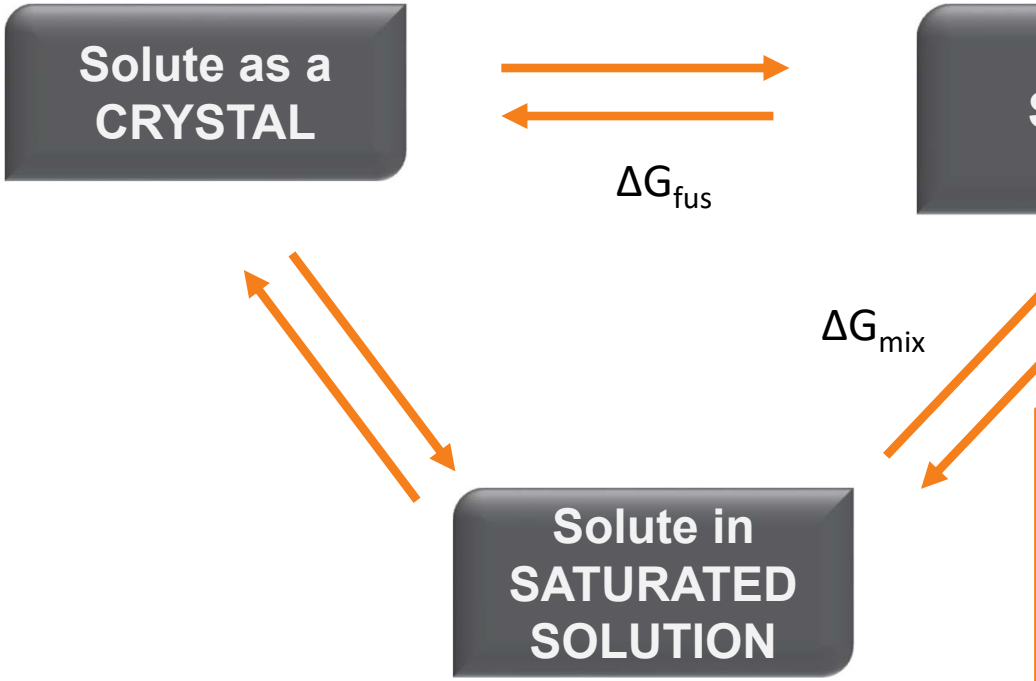
At temperature of solubility measurement:

- How happy is the solute as a crystal vs.
- How happy is the solute in liquid state

- Calculated from DSC data (ΔH_{fus} and T_m)
- Computed by some models



Modelling and Prediction



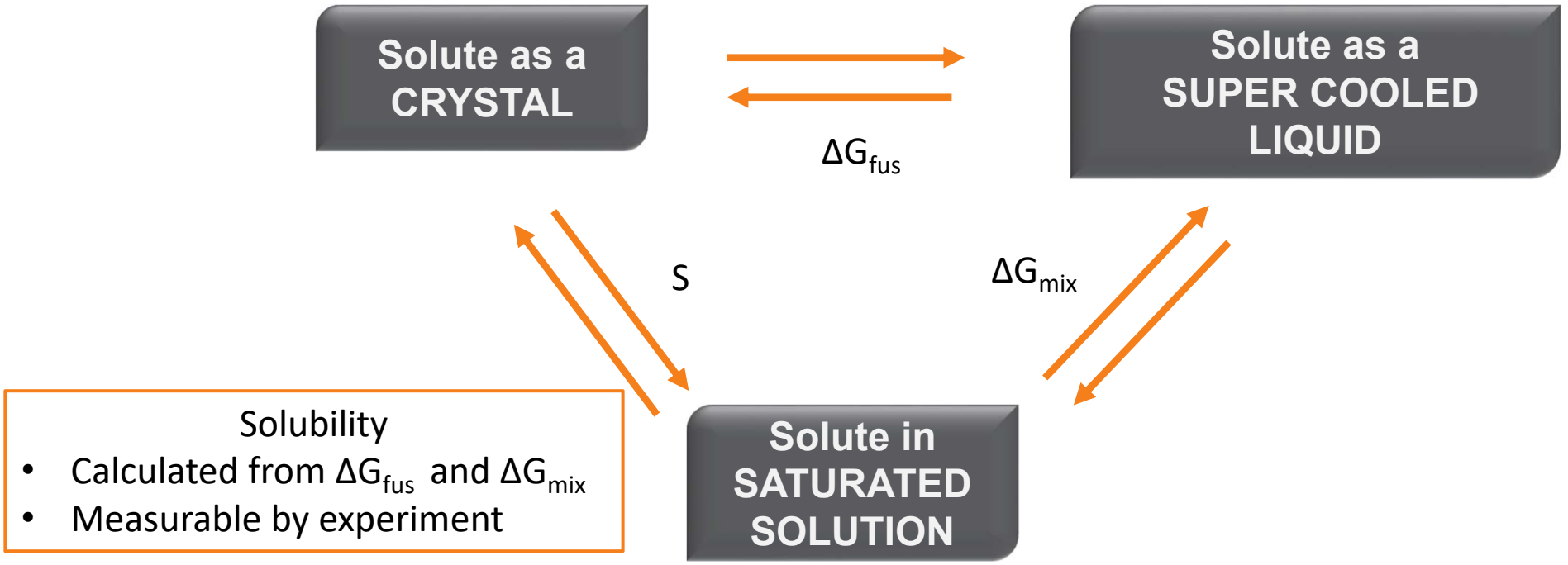
ΔG mixing

At temperature of solubility measurement :

- How happy is the solute as a pure liquid vs.
- How happy is the solute as a saturated solution

- Computed by model

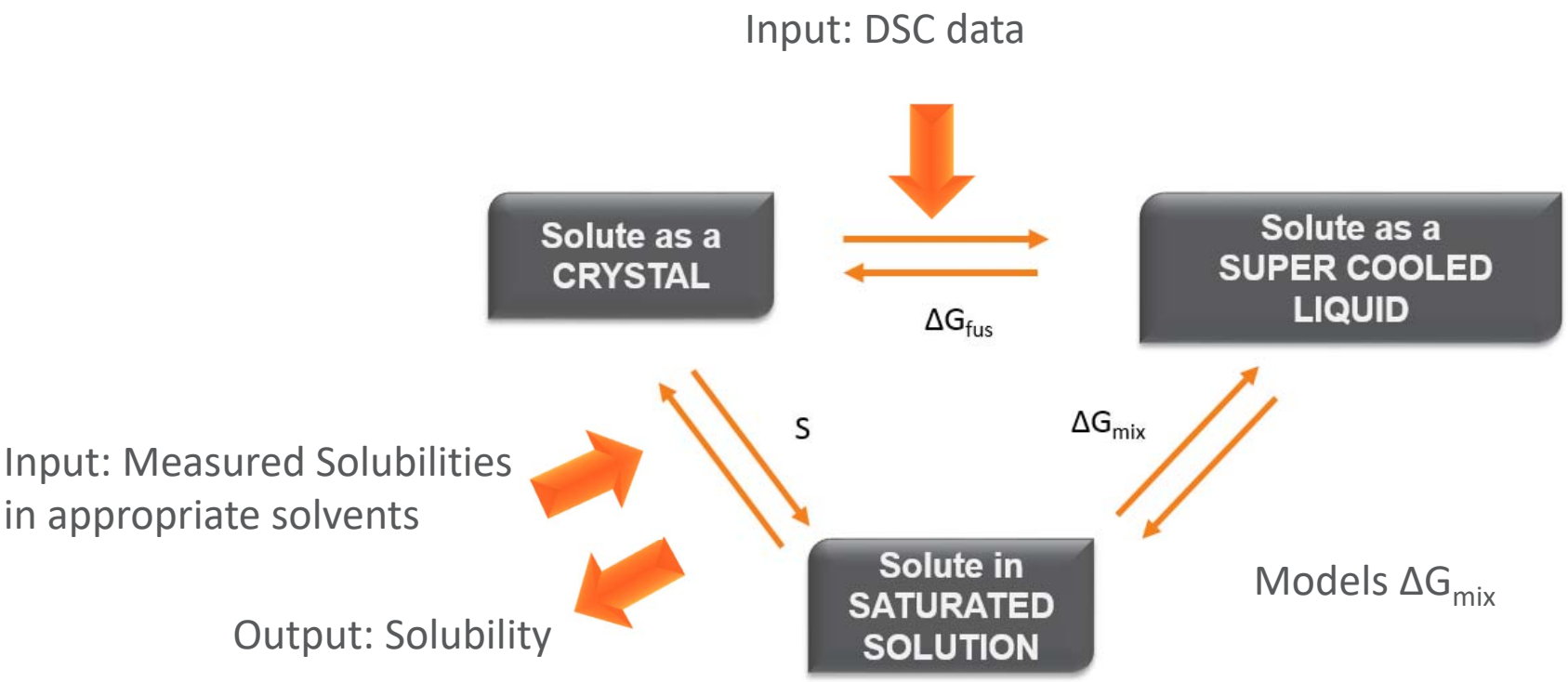
Modelling and Prediction



Solubility
- Calculated from ΔG_{fus} and ΔG_{mix}
- Measurable by experiment

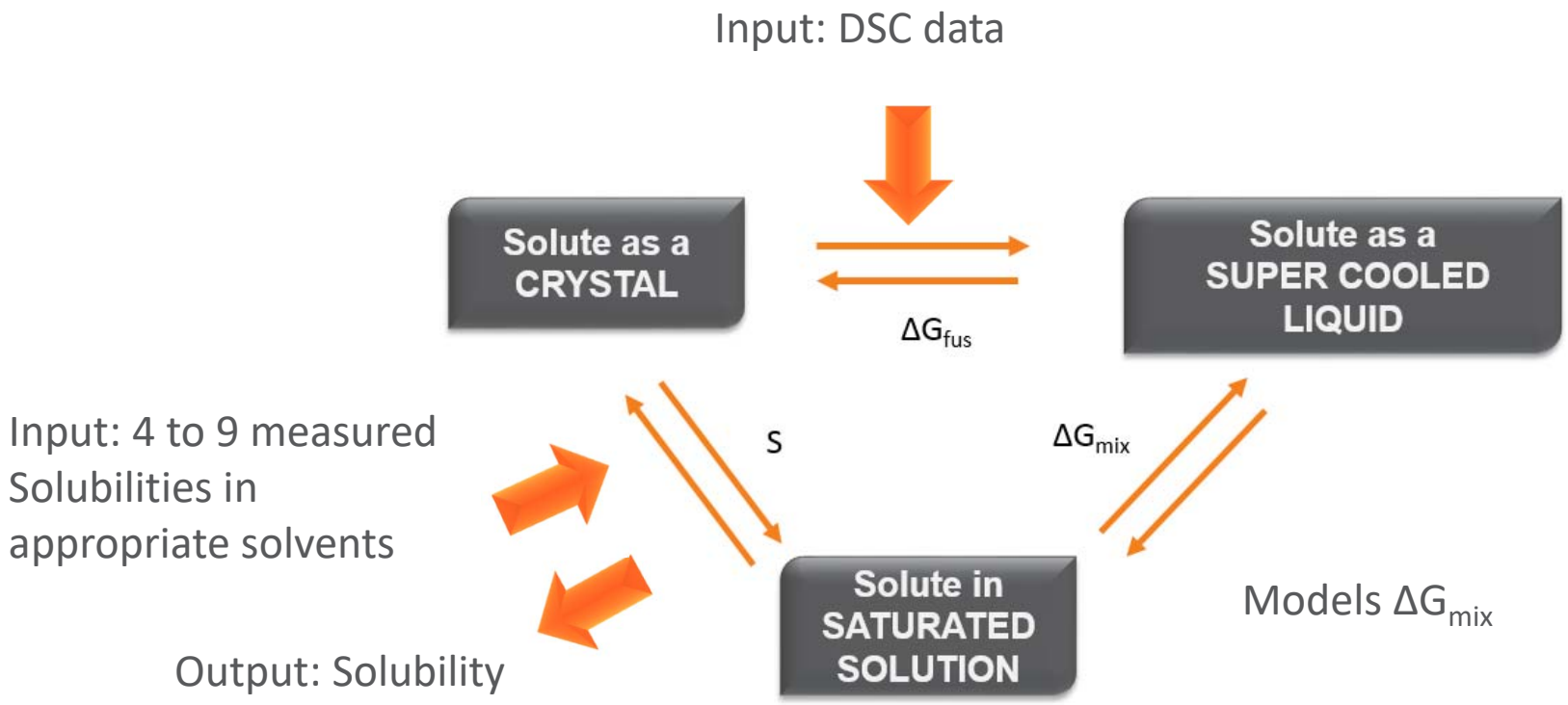
Commercial models & where they get data from

R-UNIFAC (Dynochem)



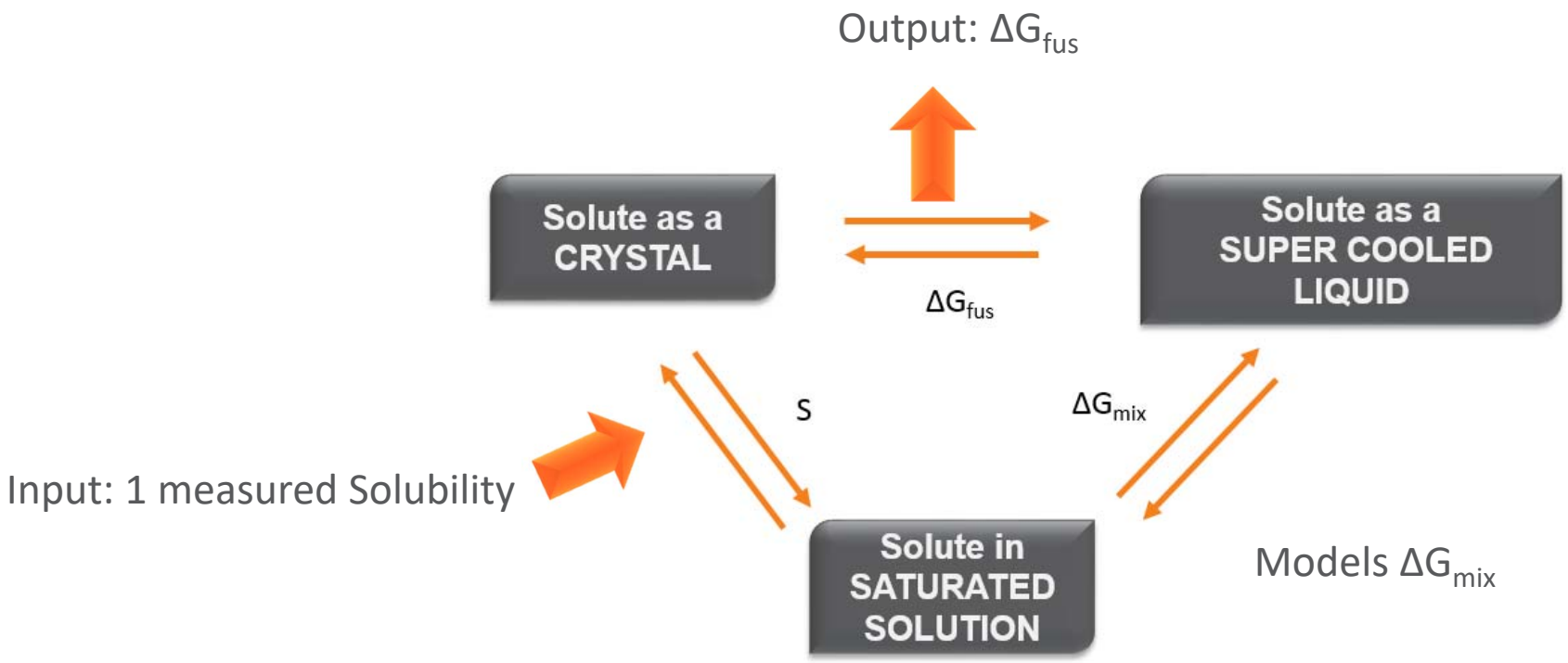
Commercial models & where they get data from

NRTL-SAC (Aspen)



Commercial models & where they get data from

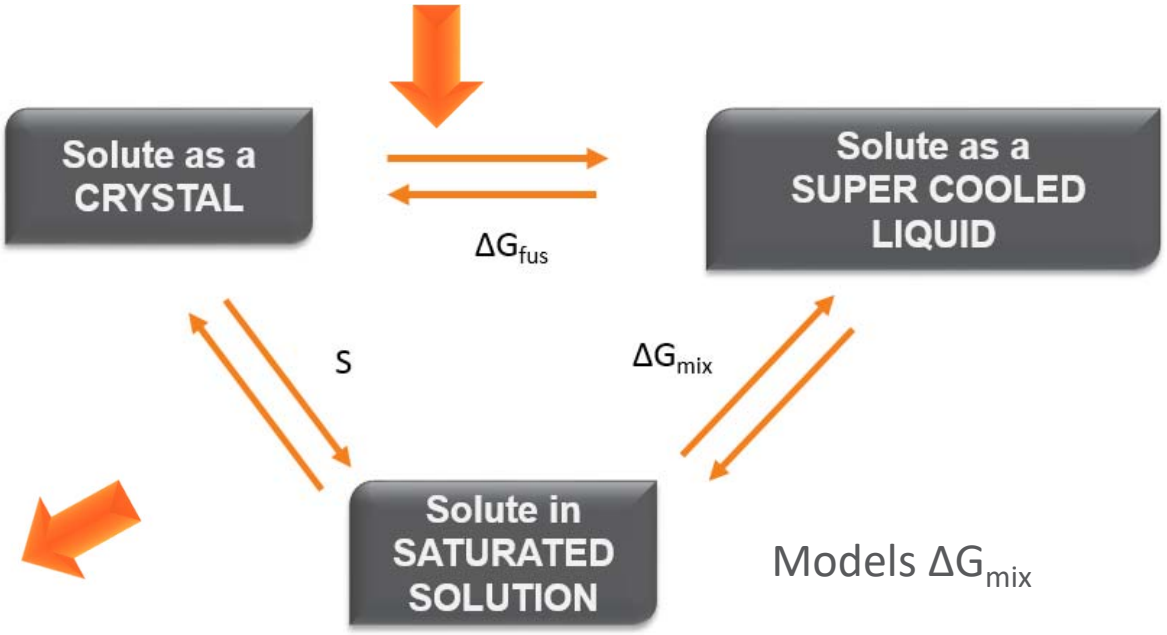
COSMO-RS (COSMOtherm) – Generate ΔG_{fus}



Commercial models & where they get data from

COSMO-RS (COSMOtherm) – For prediction

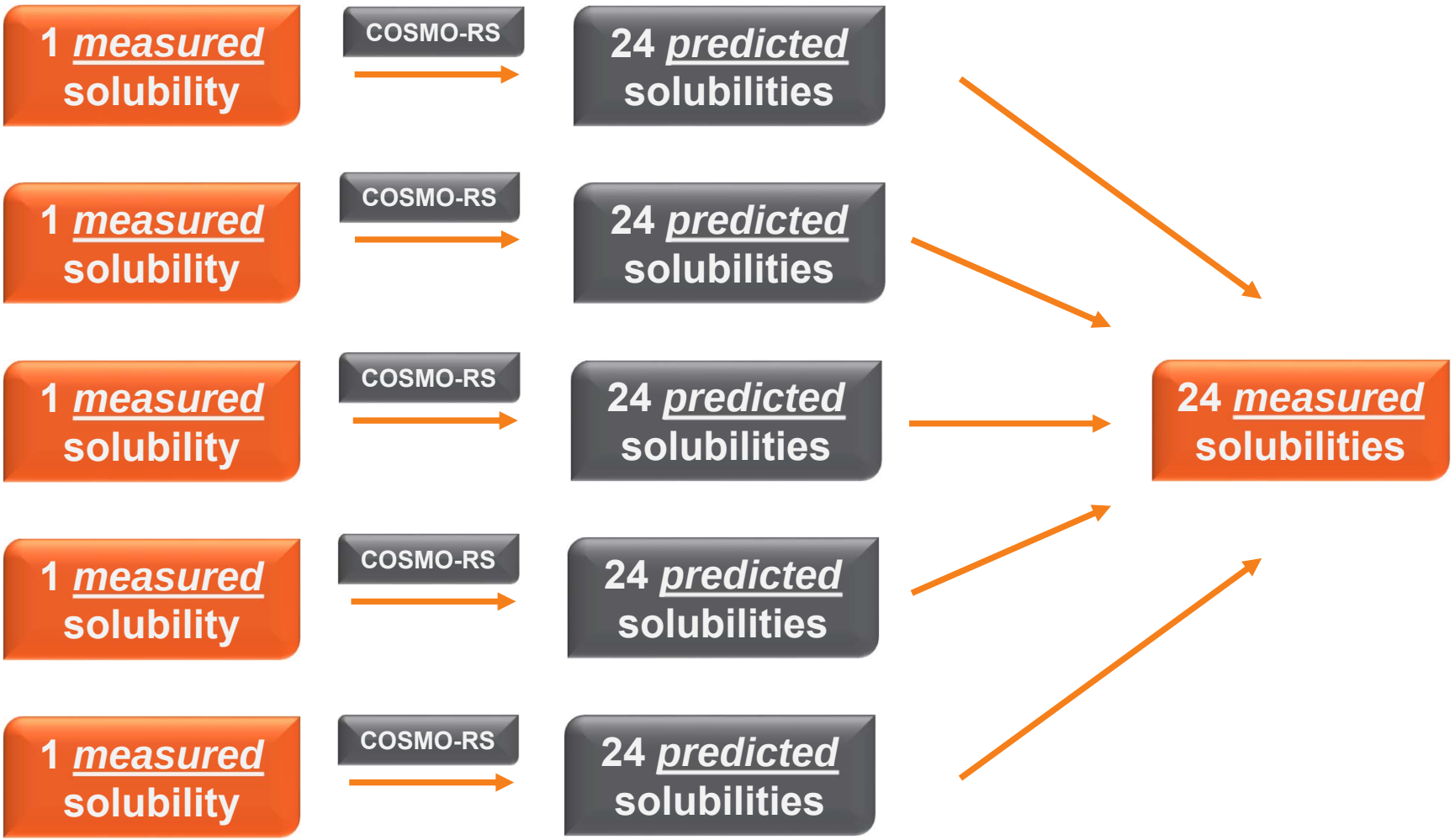
Input: ΔG_{fus} From model or DSC



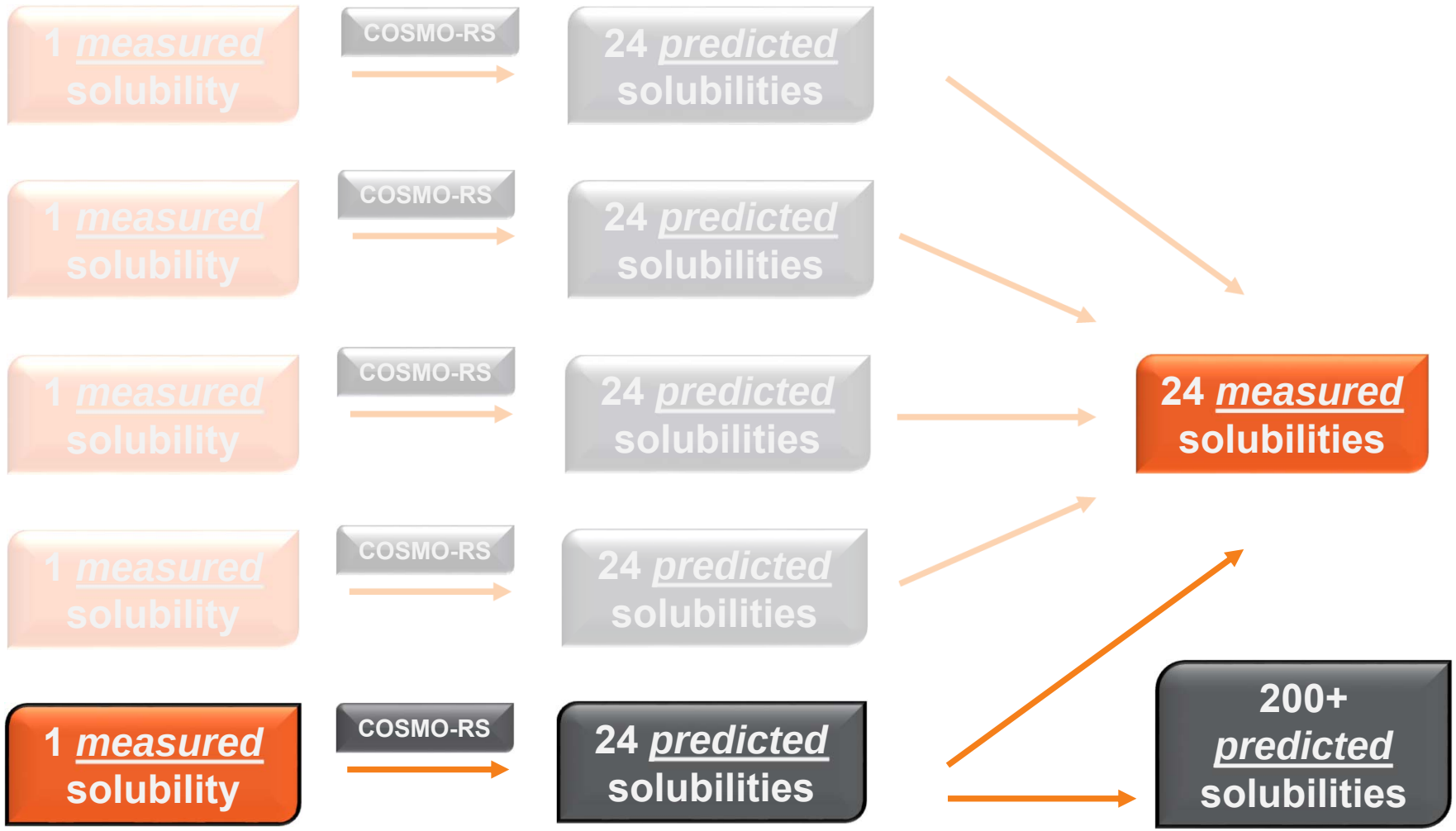
Output: Solubility

Models ΔG_{mix}

‘Fusion’ of Empirical and Prediction

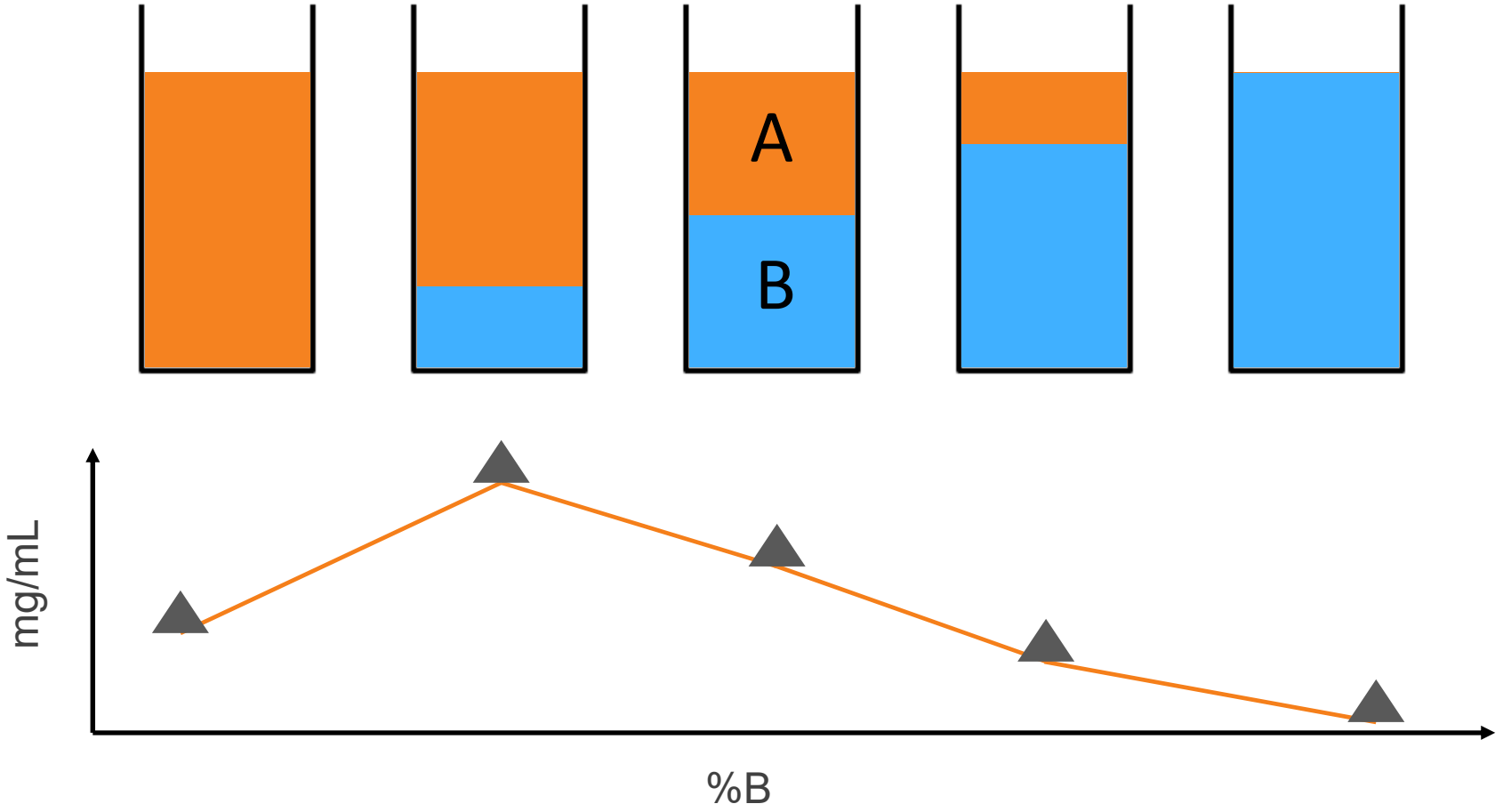


‘Fusion’ of Empirical and Prediction



00101010111100010101 – Binary Mixtures

- Modelled the same as single systems
- Harder to measure (solvent prep, evaporation)



Feed the machine

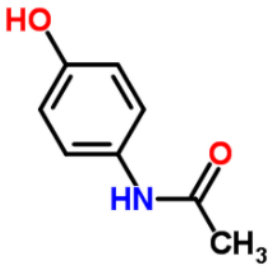
- All models need measured solubility data
  - Starting point
  - Validation
- HTE groups can produce that data
  - Helps modelling and prediction sub team
  - Helps define best practice → RFI → RFP → Next Generation Automated Solubility Platform
- Produce an experimental plan for members to undertake
- Modelling and prediction sub team also looking to mine data from other sources

Experimental

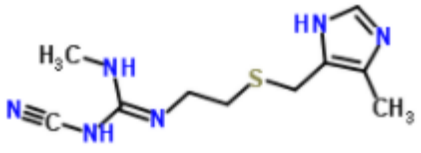
- In the process of being run…..
- All data is preliminary analysis

- 54 single solvents, 39 binary
- 25°C

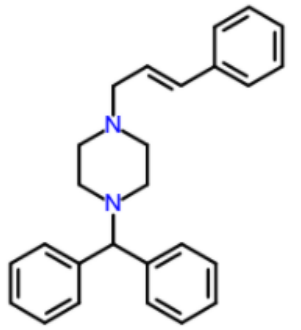
Caffeine



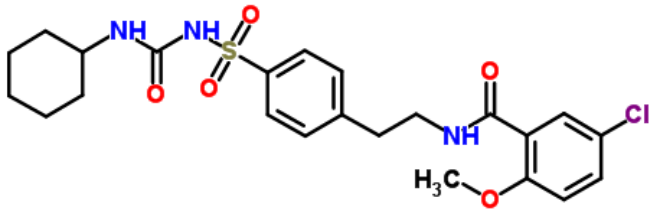
Paracetamol



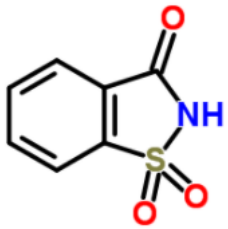
Cimetidine



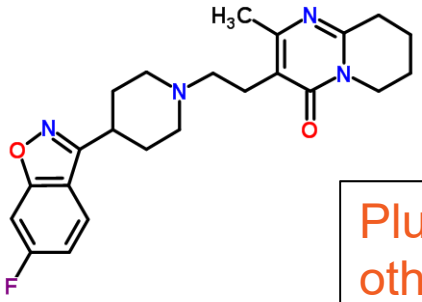
Cinnarizine



Glyburide



Saccharin

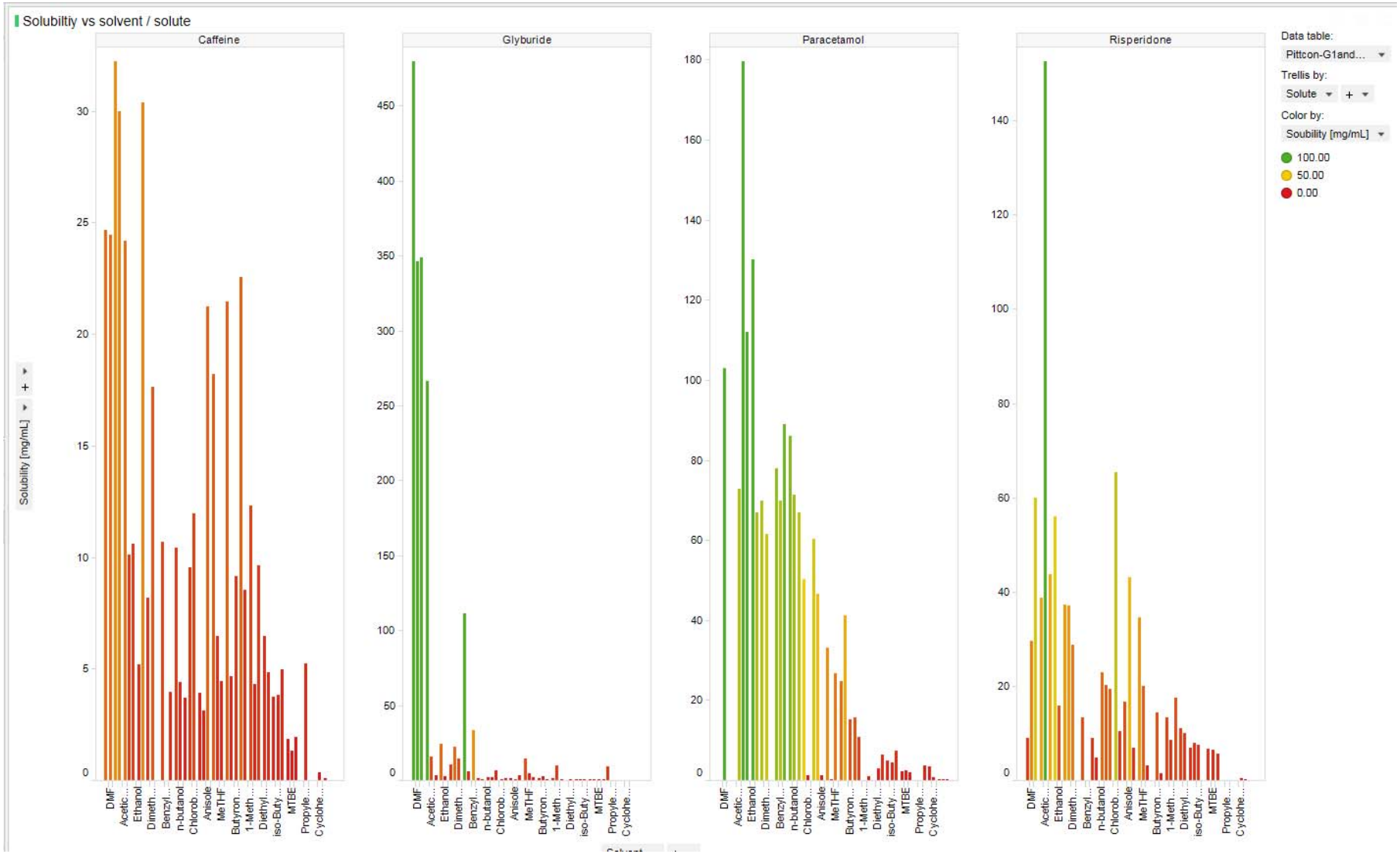


Risperidone

Plus others…

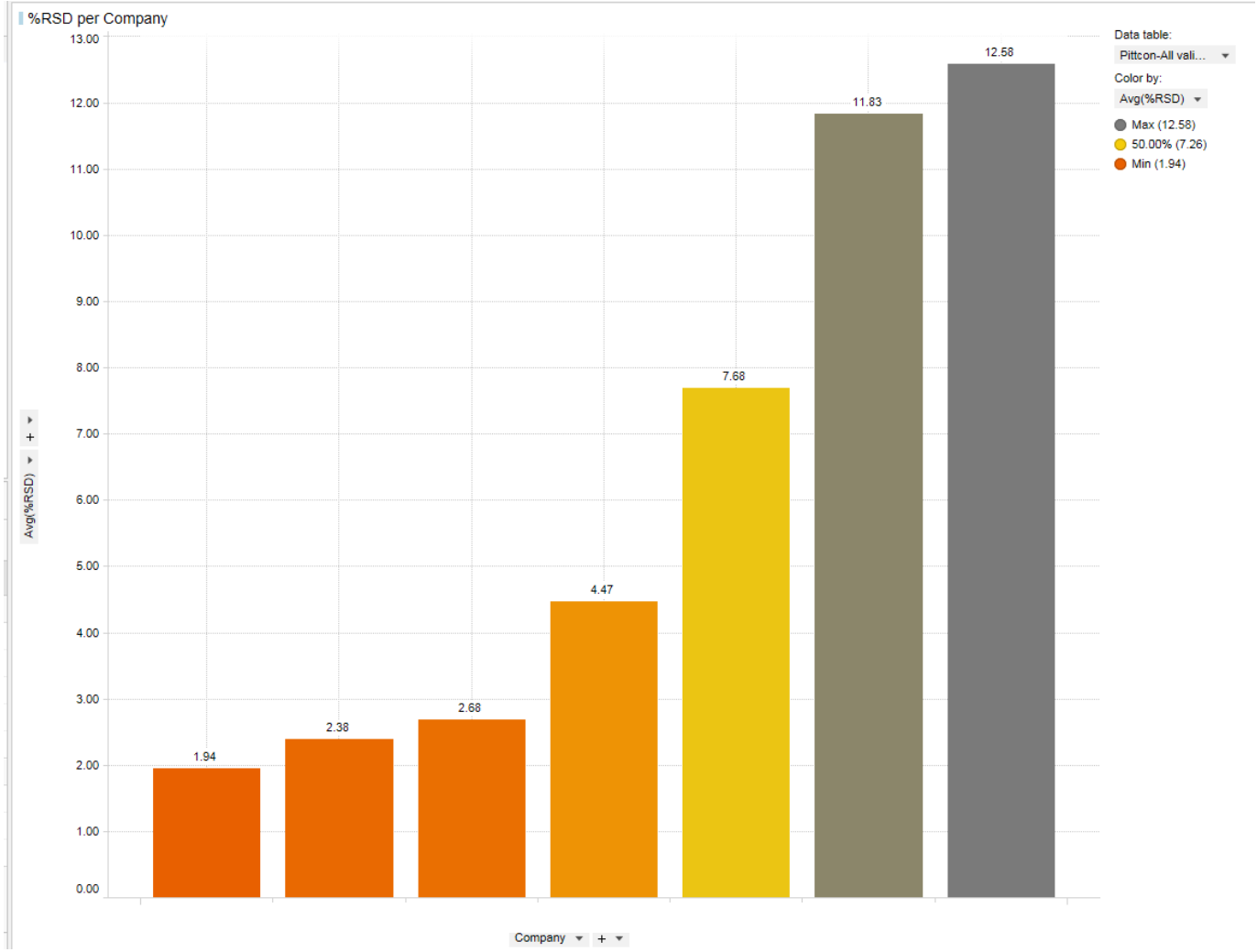
Experimental

- >4800 measurements
- Still gathering data
- Work is starting with modelling members
- Below is a subset of results



Experimental

- HTE interested in precision of methods
- Below information shows range of precision across methods



What's happening next

HTE

- RFI is out for vendors to register interest
  - Will work through and get RFP
  - 2019 for delivering working system(s)
- HTE members are working though the experimental plan

Modelling & Prediction

- Data from HTE groups being used in different models
- Looking to get data from other sources

Acknowledgments & Questions

HTE

- Lori Hilden (Lilly)
- Steve Fussell (Pfizer)
- Simon Yates (AZ)
- Chris Nunn (GSK)
- Jun Qiu (BMS)
- Rahul Sangodkar (Amgen)
- Landon Durak, Jon Truong (Takeda)
- Alex Chin (Merck)
- Cindy Qin (BI)

Modelling & Prediction

- Simone Tomasi, David Hose (AZ)
- Steve Fussell, Jason Mustakis, Yuriy Abramov (Pfizer)
- Ravi Ananthula, Jeff Tan (Lilly)
- Rahul Sangodkar, Mike Lovette (Amgen)
- Eric Sirota, Alex Chin, Anthony Diaz-Santana (Merck)
- Frank Ricci (BI)
- Jacob Albrecht (BMS)