## Introduction and motivation

Initial experimental phases of crystallisation process development are commonly carried out at very small scales, typically using 1-5 mL vessels, with the aim of selecting a:
- solvent based on solubility
- crystal solid state

These activities are commonly conducted in high throughput reactor systems, such as the Crystalline (Technobis Crystalization Systems).

For the development, validation and optimization of crystallisation process models this data is typically not utilized and the selected solution system is probed experimentally and more quantitatively at much larger scales, typically between 100 – 1000 mL.

A more quantitative usage of the data generated at small scale for the development of process models which may significantly reduce the number of larger scale experiments required, would aid in addressing the increasing constraints on time and materials in pharmaceutical development.

## Typical raw Crystalline data

Sample turbidity and block temperature are recorded throughout. Addition of an in situ camera module allows for the imaging of suspended particles and the determination of particle size distribution (PSD) through image analysis.

## Comparison to at scale parameter estimation

<table>
<thead>
<tr>
<th>Experimental scales &amp; systems</th>
<th>Estimation at microscale</th>
<th>Estimation at 1 L scale</th>
<th>Estimation at microscale with refinement at 1 L scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscale experiments (5 mL each)</td>
<td>8 (as part of solubility measurement)</td>
<td>-</td>
<td>8 (as part of solubility measurement)</td>
</tr>
<tr>
<td>1 L scale experiments</td>
<td>-</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Total API usage</td>
<td>4 g</td>
<td>1200 g</td>
<td>520 g</td>
</tr>
</tbody>
</table>

## Summary

- Initial estimates of crystallisation kinetics parameters can be obtained at the microscale as part of typical solubility measurement experiments.
- Through sensitivity analysis, mechanism discrimination can be performed to identify the most dominant crystallisation phenomena.
- Using these initial estimates a 57 % reduction in API usage can be achieved when compared with estimating parameters solely at lab scale (1 L).

## Mechanism discrimination

Enabling mechanism discrimination through sensitivity analysis at an earlier stage of process development.

### Primary nucleation

**Agglomeration**

### Secondary nucleation