Save money with mixing simulation studies !

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To meet today's quality by design standards Hovione has gained a new ally in process development and troubleshooting. The use of VisiMix®, a sophisticated mixing simulation technology is allowing chemists and process engineers to gain comprehensive insights on vessel mixing performance.

Decisions on choosing the right vessels and adequate equipment modifications for scale-up are made efficiently and based on quantitative data. On the other hand troubleshooting and process optimization has been made easier trough using simple scale-down strategies for laboratory research

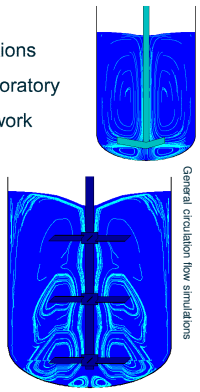
To date Hovione has used this promising new tool to study over ten processes.

Efficient process development

- Laboratory tests more similar to manufacturing conditions
- Manufacturing problems can be anticipated at the laboratory
- In *silico* approach can avoid extensive experimental work

Reduced manufacturing costs

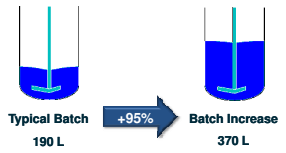
- Decreased probability for batch failure
- Simpler solutions can be found in detriment of more complex ones



Challenge 1 – Increasing the batch size of a sensitive crystallization

- The objective was to increase the batch size of a solvent/anti-solvent crystallization inside the same vessel maintaining the very narrow and sensitive particle size distribution.

Bigger batches result in a faster campaign



Crystal PSD Controlled Parameters				
D_v10	D_v50	D_v90	D_v90/D_v10	D_v50/D_v10

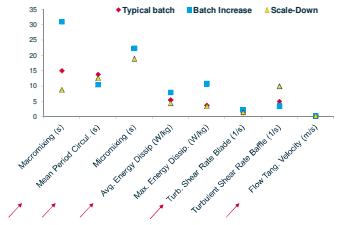
The vessel geometry and impeller speed are critical for PSD!

Simple scale-down strategy

Evaluation of the manufacturing mixing profile
Single-Phase Mixing
Energy Dissipation
Turbulence Shear Rates

Laboratory experiments variables
Reactor Geometry
Batch Size
RPM
Inlet Position

Evaluation of mixing parameters



The more important parameters (red arrows) are kept constant by selecting the adequate stirring speed for each batch.

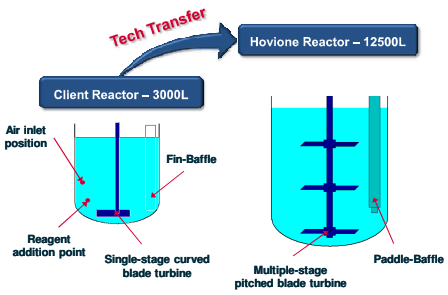
The lab scale-down experiment and the batch increase at manufacturing were **successful!**

6 batch campaign is now made in 3 batches!

Challenge 2 – Optimizing reagent blending and air inlet position

- In this process tech transfer the client pointed out for the need of "good mixing" during a reagent addition. Additionally an oxidation reaction was also evaluated in order to select the best air inlet position.

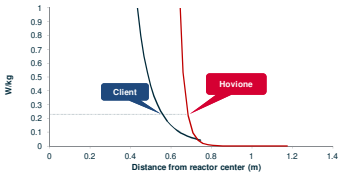
Different reactor geometries: Client *vs* Hovione



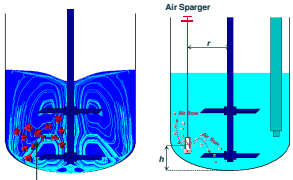
Evaluation of mixing parameters

	Reaction Volume (L)	RPM	Micromixing (s)	Circ. Flow Rate (m^3/s)	Max. Energy D. (W/kg)
Client	2500	75	4.3	0.376	32
Hovione	8000	60	3.43	0.391	5.39

Energy dissipation at addition point



Reagent addition point and air inlet position considerations

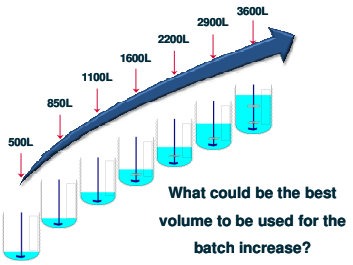


Client remained confident. Operation was a **success!**

Right First Time!

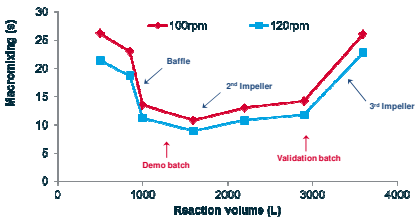
Challenge 3 – Evaluation of a cryogenic process to avoid potential mixing problems

- Since this reaction was carried at very low temperatures and exhibited high viscosities, simulations were made to avoid potential reagent freezing issues.



What could be the best volume to be used for the batch increase?

Overall mixing time for several reaction volumes



Mixing performance considerations

Based on the overall mixing time the adequate reaction volume was set below the 3rd impeller stage.

Increasing the stirring speed to 120rpm is advisable upon batch increase.

Client **approved batch increase.** Validation campaign **successful!**

Goals Achieved!

A Real Return on Investment

Inadequate mixing conditions can destroy months of efforts on process development. Improving the understanding of the mixing phenomena has already proved to have a real return on investment for it allows more robust and predictable manufacturing processes.

