CORNING

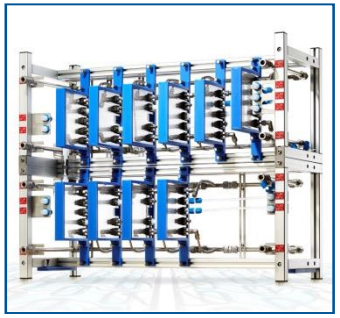
Advanced-Flow Reactors: Made for Industrial Productions

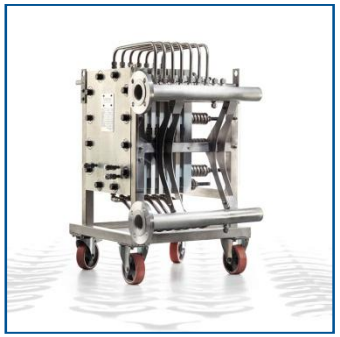
Marc Winter and Alessandra Vizza, Corning, France

RSC Symposium Chemspec Europe 2017
Munich, 2017 June 1st

Presentation Outline

1. Introduction
2. Seamless Scale-Up
3. Industrial Examples
4. The Challenge of Solid handling
5. Outlook





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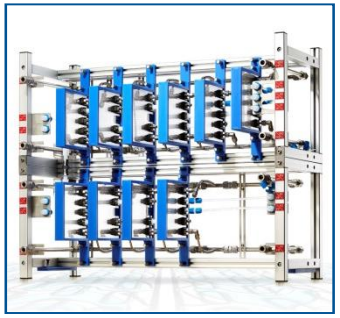
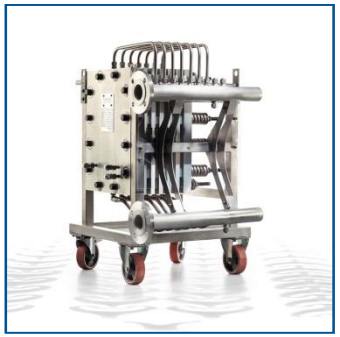




About Corning

Founded:
1851

Headquarters:
Corning, New York

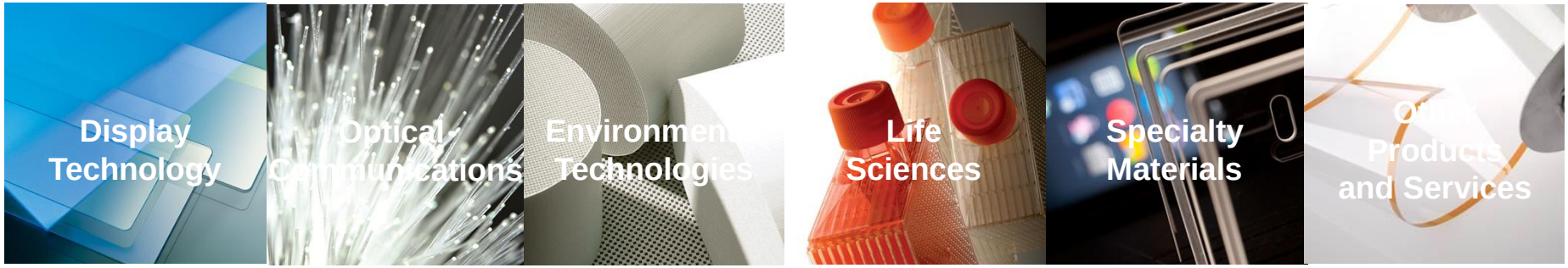
Employees:
40,000 worldwide

2016 Sales:
~$ 9;7 billion

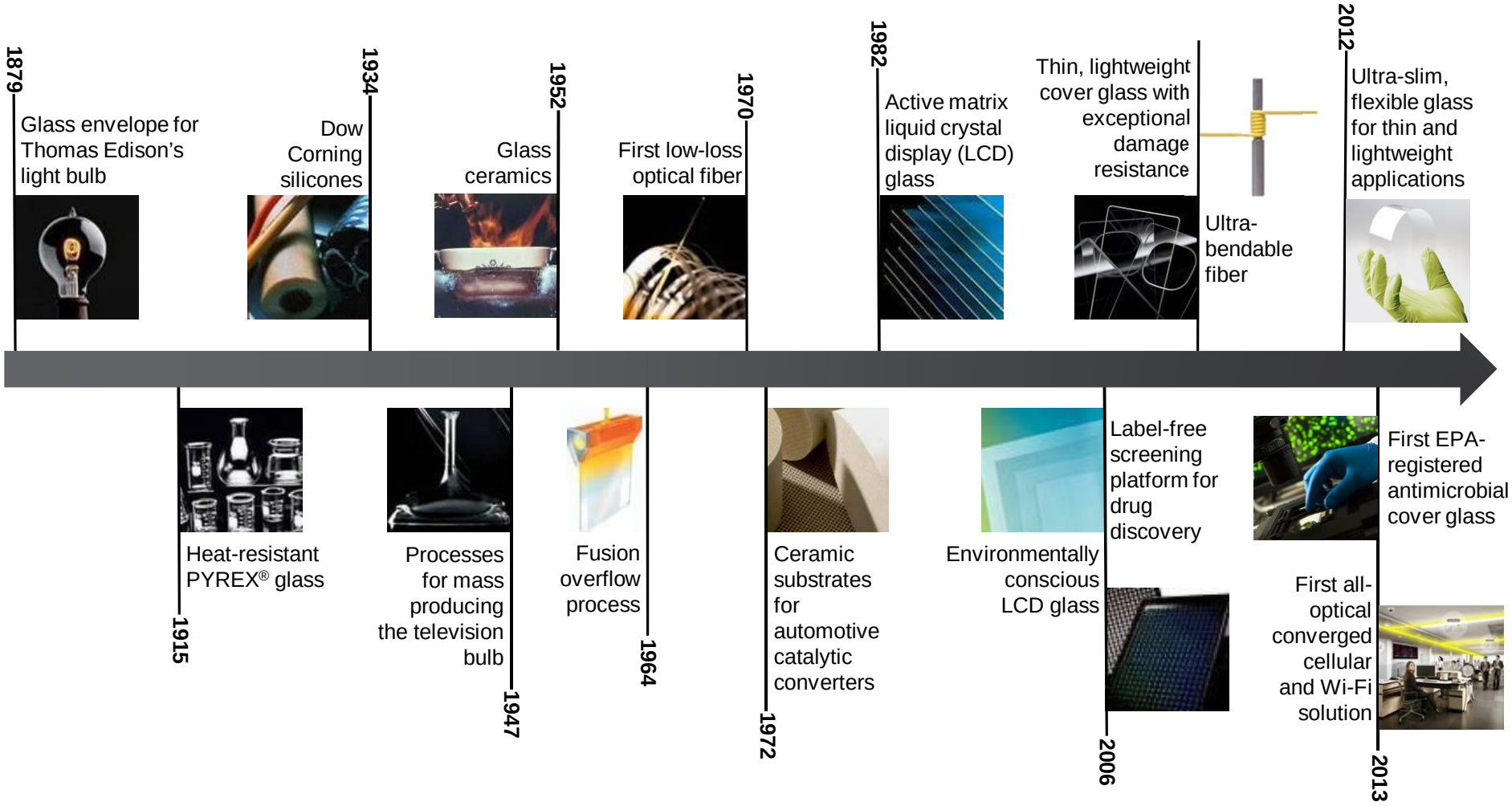
Fortune 500 Rank (2016):
313

Corning is one of the **world's leading innovators in materials science**. For more than160 years, Corning has applied its unparalleled **expertise in specialty glass, ceramics, and optical physics** to **develop products that have created new industries and transformed people's lives**.

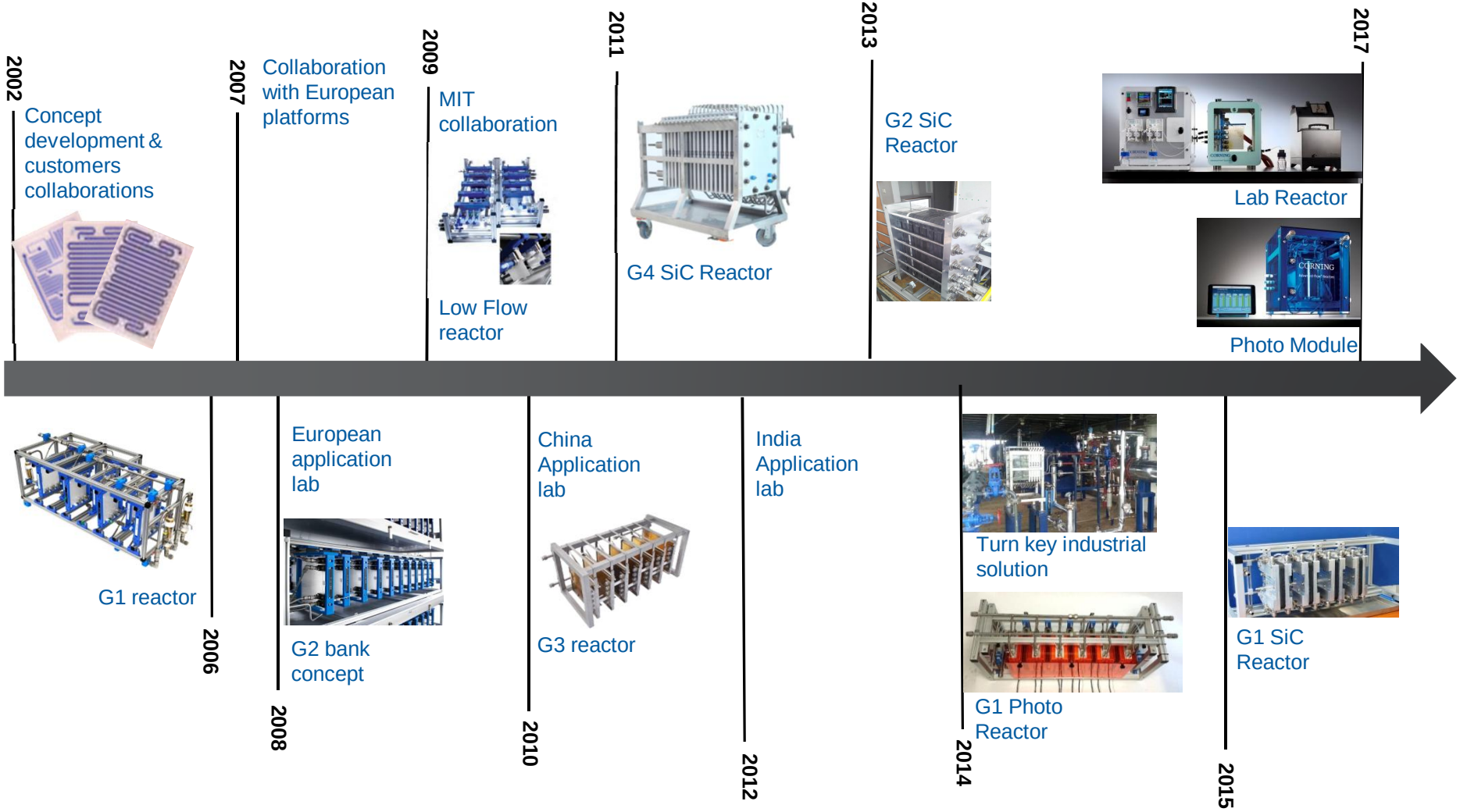
Corning succeeds through: sustained investment in **R&D**, a unique combination of **material and process innovation**, and **close collaboration with customers to solve tough technology challenges**.



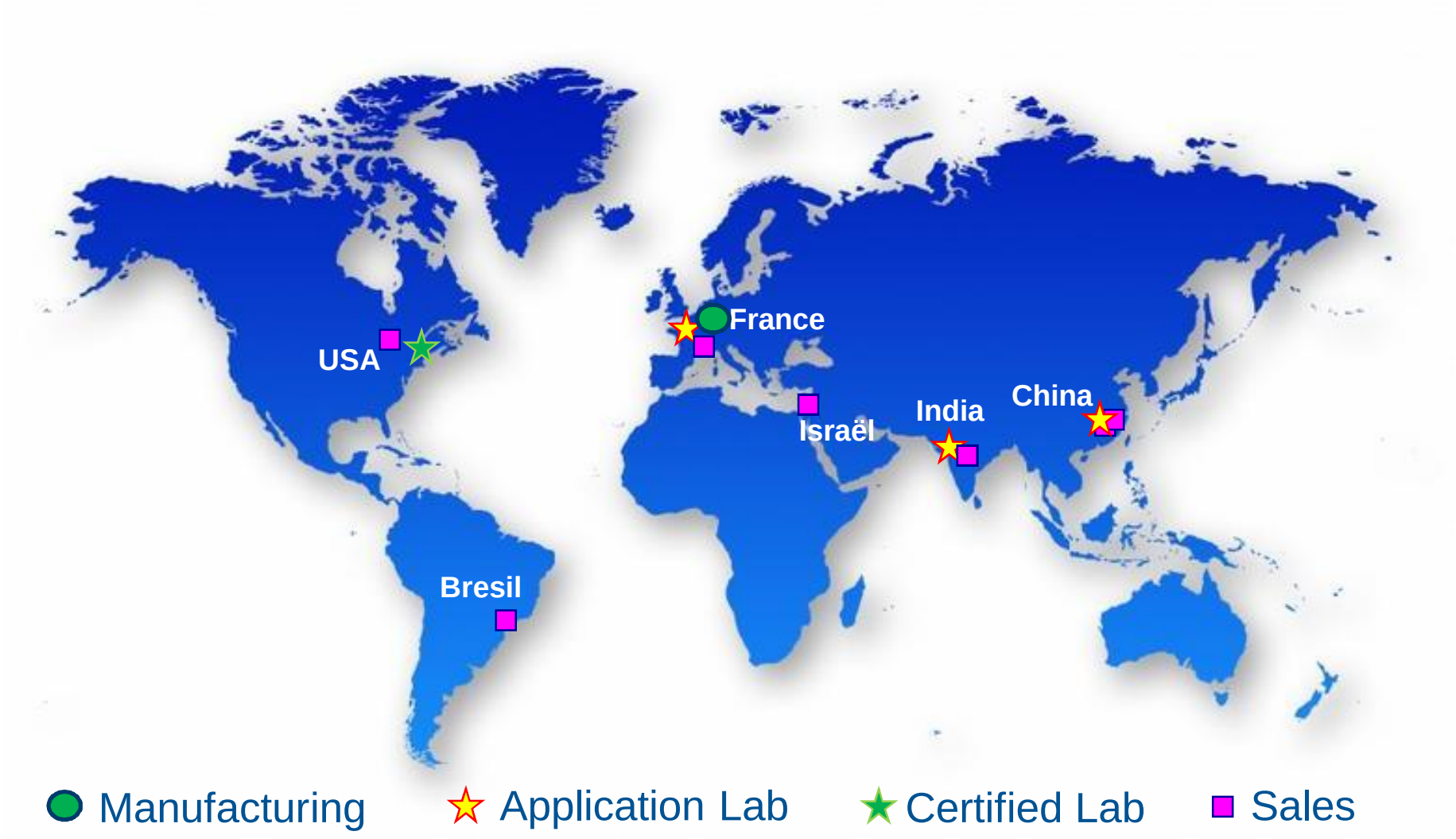
Corning's continuous flow reactors build on the company's 160 years of innovation



History of Corning Reactor Technologies: More than one decade of expertise



A worldwide presence

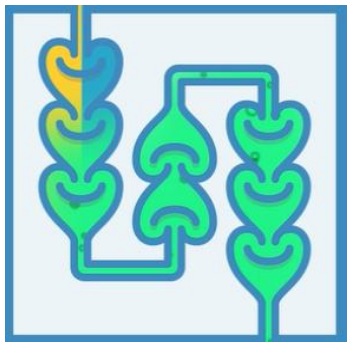


Corning® Advanced-Flow™ Reactor Value Proposition

Revolutionary Improvement vs. Batch

Corning AFR: Unique concepts and advantages

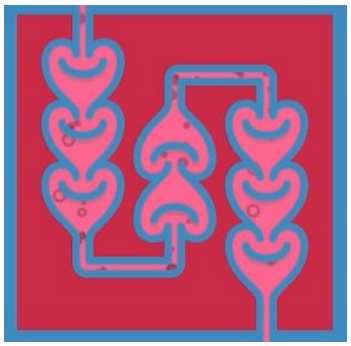
High Mixing



Patented HEART shape

Ideal for immiscible and multiphase systems

High Heat Exchange



Combines heat exchange and reactive path in a sandwich structure

Independent thermal control

Durable Materials

Glass and Ceramic

Superior corrosion resistance

Seamless Scale-Up

Reactors are designed for seamless scale-up

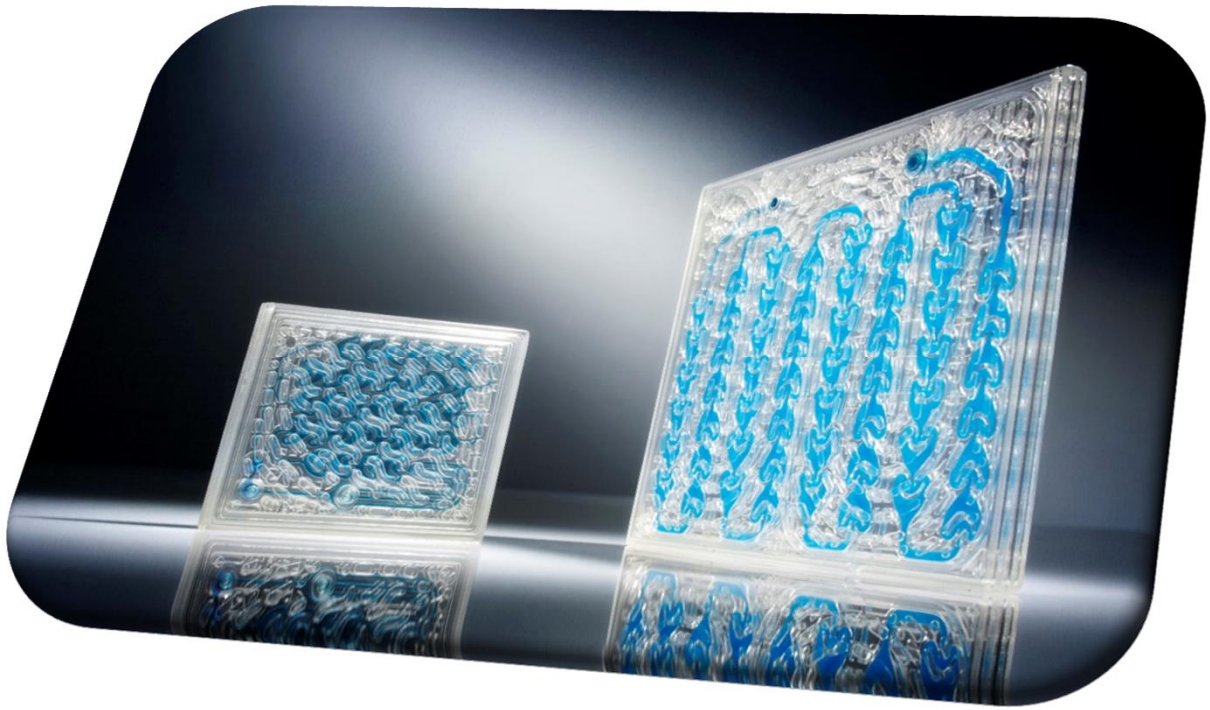
Direct from Lab to Production

Complete Units

Complete turn-key solutions

Engineered and customized units

The unique concept of a Fluidic Module

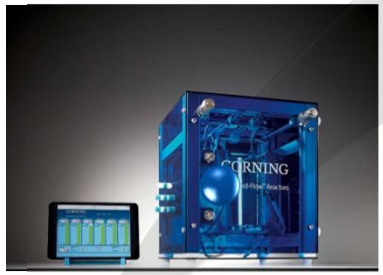


Increase throughput with similar:

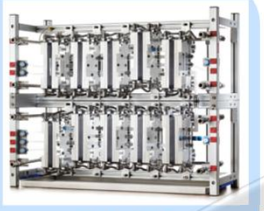
- Mixing
- Residence time distribution
- Heat Exchange
- Mass transfer in heterogeneous systems

Comprehensive Solutions from Lab, to Process Development, and to Industrial Production

Lab scale stepping into flow chemistry, Application process development



Application Process Development & Small Production



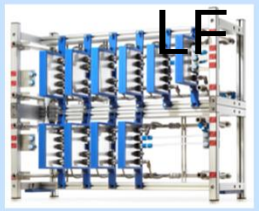
G1 SiC

80 t/y

G1

G1 Photo

LF



G1 Glass

250 t/y

G2

G2 SiC

1000 t/y

G3

G3 Glass

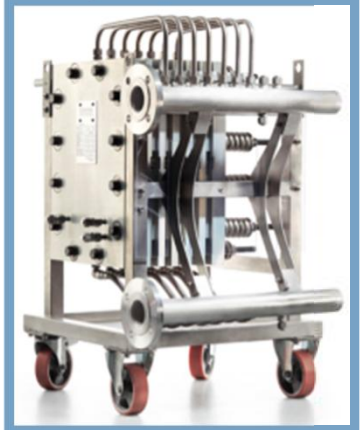
Industrial Production

2000 t/y

G4

3500 t/y

GP4

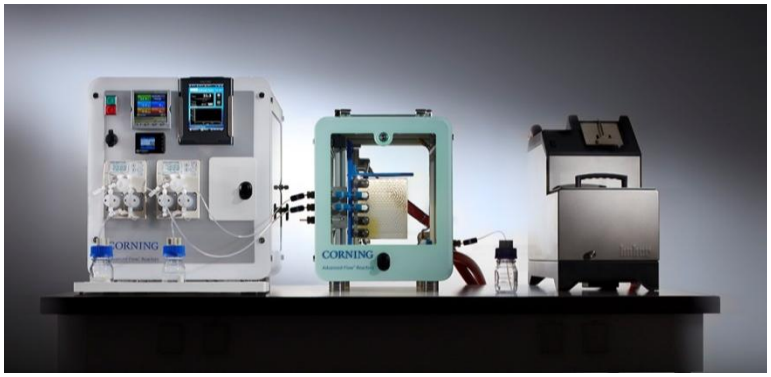


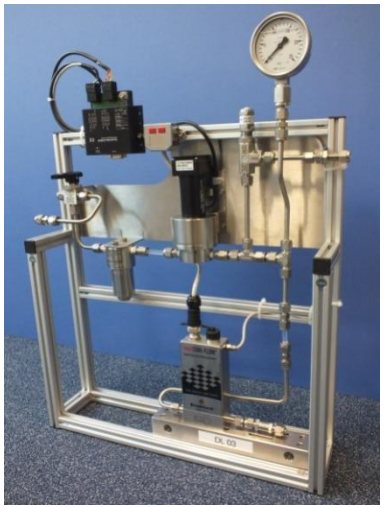
SiC

Auxiliaries – Up Stream Process

- Up Stream process is an important part of the success in Flow Chemistry
- Accuracy of the flow is a key parameters
  - Simple HPLC pumps
  - To more complex Dosing Lines
- Heat Exchanger will allow to reach full potential of Volumetric Heat transfer
- Other solution could be added such as: electrical heat tracing, safety valve, sensors, etc.

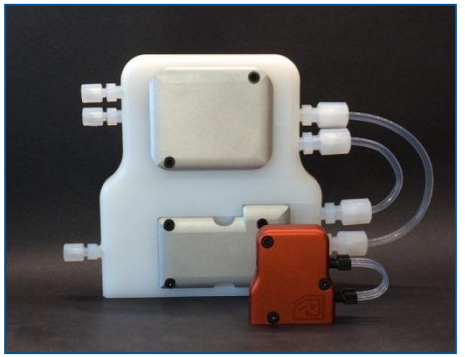
Auxiliaries – Up Stream Process





Auxiliaries – Down Stream Process

- Less critical than the up-stream process, but will allow optimisation of the global system
- Several step could be added after the reactor
- Online/Inline analytics:
  - Quick answer during development
  - Allow automatisation
  - Follow-up of critical parameter during production



**Pictures from Marqmetrix, Magritek and Zaiput*

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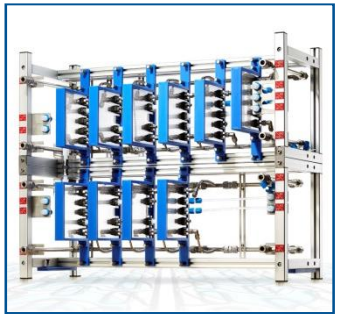
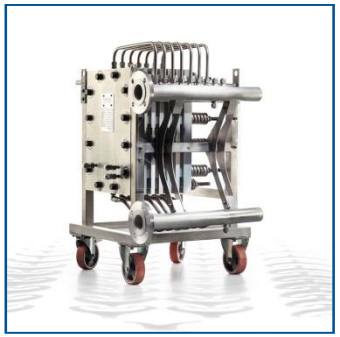




What is really a Seamless Scale-Up?

A seamless scale-up will be achieved, when moving form a small continuous reactor, to a larger one, if you apply the same parameter as in lab (temperature, residence time, concentration, stoichiometric ratio), you will get the same result in production (conversion, yield, impurity profile…)

A seamless scale-up do not require any pilot study, nor any process optimization. It is a straightforward process, that does not require much time.

How to demonstrate a seamless scale-up???

As nearly every chemical reaction is specific (mixing or temperature sensitive, fast, exothermic or not, with concurrent reactions, parallel ….), making a specific reaction “seamless” does not mean at all that the scale-up will be always seamless.

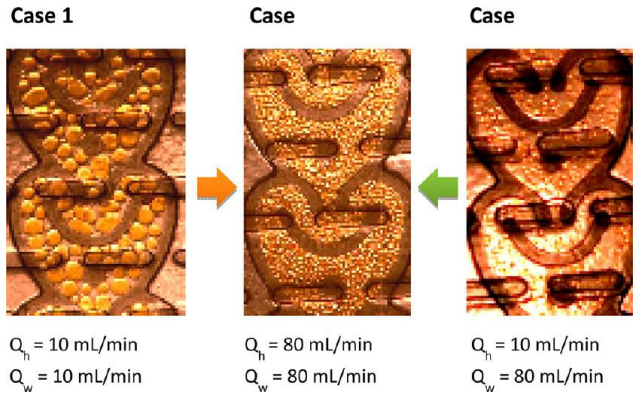
Chemist to Chemical Engineering

Reactor capabilities	Reaction's need
MIXING / MASS TRANSFER	Contact between the molecules of the reactants
Residence Time	Keep the molecules in contact during a sufficient time to allow the completion of the reaction
Residence Time Distribution	Does not keep the molecules to many time in contact to avoid side reactions
HEAT TRANSFER	Isothermal condition / reaction enthalpy release

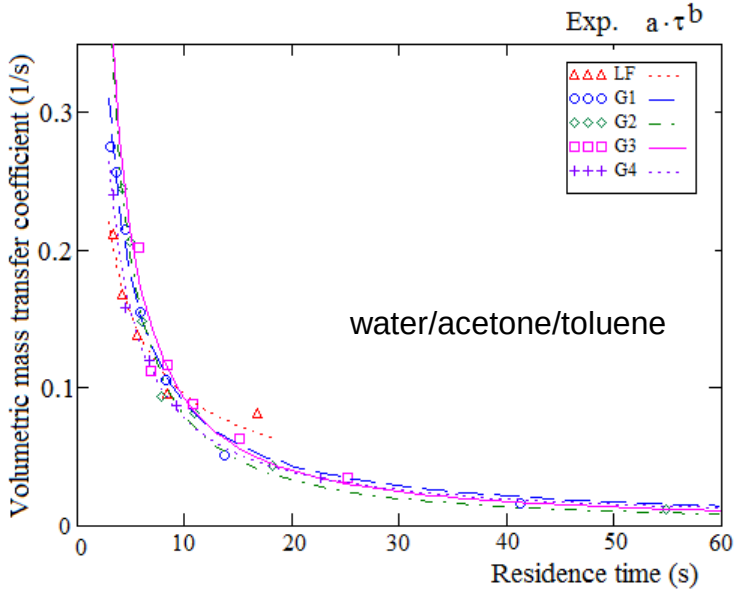
Volumetric mass transfer coefficient: A seamless scale-up

Patented HEART-shape design:

- Superior mixing performance in multiphase systems[1]
- Higher performances in L/L mass transfer coefficient ($k_L a$)[2]
  - Up to 10^3 compared to packed column
  - 2x - 4x better than other “micro-channel” devices



[1] M. José Nieves-Remacha, A.l A. Kulkarni, K. F. Jensen, **Hydrodynamics of Liquid−Liquid Dispersion in an Advanced-Flow Reactor**, *Ind. Eng. Chem. Res*. 51,16251 – 16262 (2012)

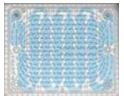
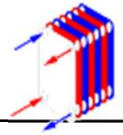
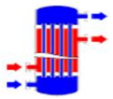
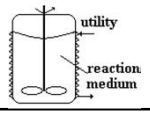
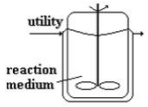


Similar mass transfer performances from lab to production

[2] D. Lavric, C. Cerato-Noyerie, P. Woehl, F. Zhang, **Multiphase systems: Enhanced Mass fluxes in Corning®-advanced-flow™ reactors**, IMRET 12, Lyon, France (2012)

Heat transfer coefficient
~100x-1000x higher than batch

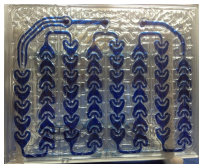
Seamless scale-up: similar heat transfer coefficient from G1 to G4

Method		Volumetric heat transfer coefficient (MW/m^3K)
Ceramic SiC fluidic modules		1.5
*Corning glass fluidic modules (water/water, ~ 0.7 m/s)		1.6
*Plate (*metallic*, 4 mm spaced; water/water, 1 m/s)		1.25
*Shell and tubes (*metallic*; water/water; 1 m/s)		0.2
*Batch with external heat exchanger		10^{-2}
*Jacketed batch		10^{-3}

*D. Lavric, **Thermal performance of Corning glass microstructures**, Proceedings of the *Heat Transfer and Fluid Flow in Microscale III* Conference, Hilton Whistler, BC, Canada, ECI international, 2008

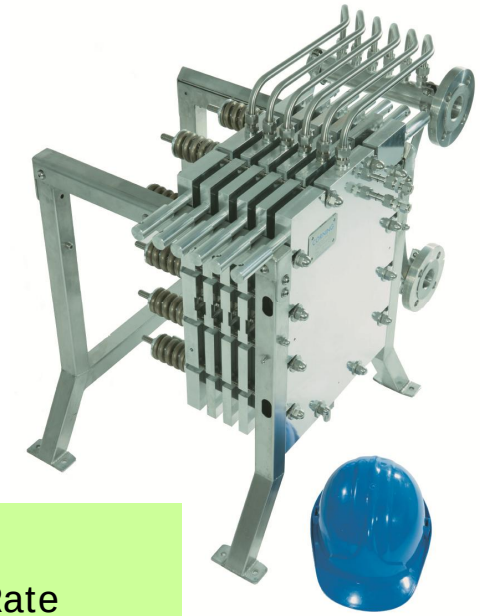
Scale-up Principle：Same Residence Time

G1 Platform



Channel size：~1mm; Internal Volume: 8 ml

G4 Production



Channel size: ~5mm; IV = 250 ml

Reactor Residence Time

= Reactor Internal Volume ÷ Mixture Volumetric Flow Rate

G1 Case：

Reactor Volume = 6FM x 8ml/FM = 48 ml

Mixture flow = 150 ml/min

= 9 l/h

= 64,8 m^3/yr

Residence time = 48 ÷ 150 = 0,32 min = 19,2 s

G4 Case：

Mixture flow = 2 160 m^3/yr

= 300 l/h

= 6 000 ml/min

Residence time = 19,2 s = 0,32 min

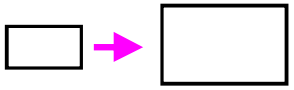
Internal V =0,32 x 6000 = 1920 ml

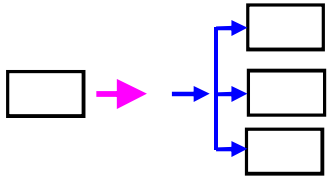
# of FMs in reactor = 1920 ÷ 250 = 8

Scale-up from G1 to G4 and numbering-up

Yearly throughput: 5 000 t/y
Yearly production: 2 200 t/y
2 G4 reactors in parallel

Production increase versus lab :
100 time higher





10 minutes after start-up ,
the product was on specs
(purity > 99,6%)

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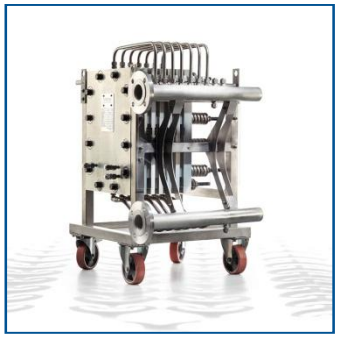
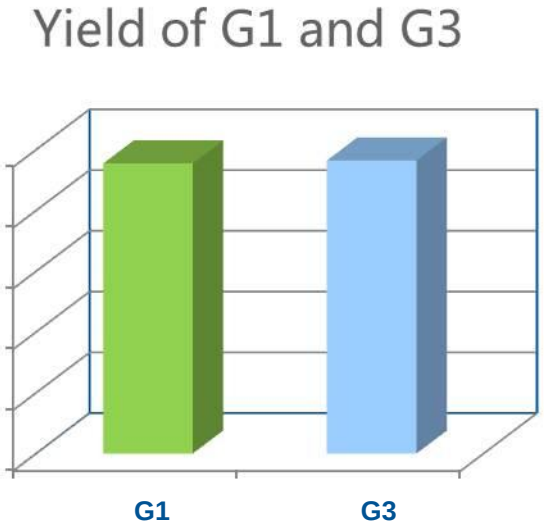
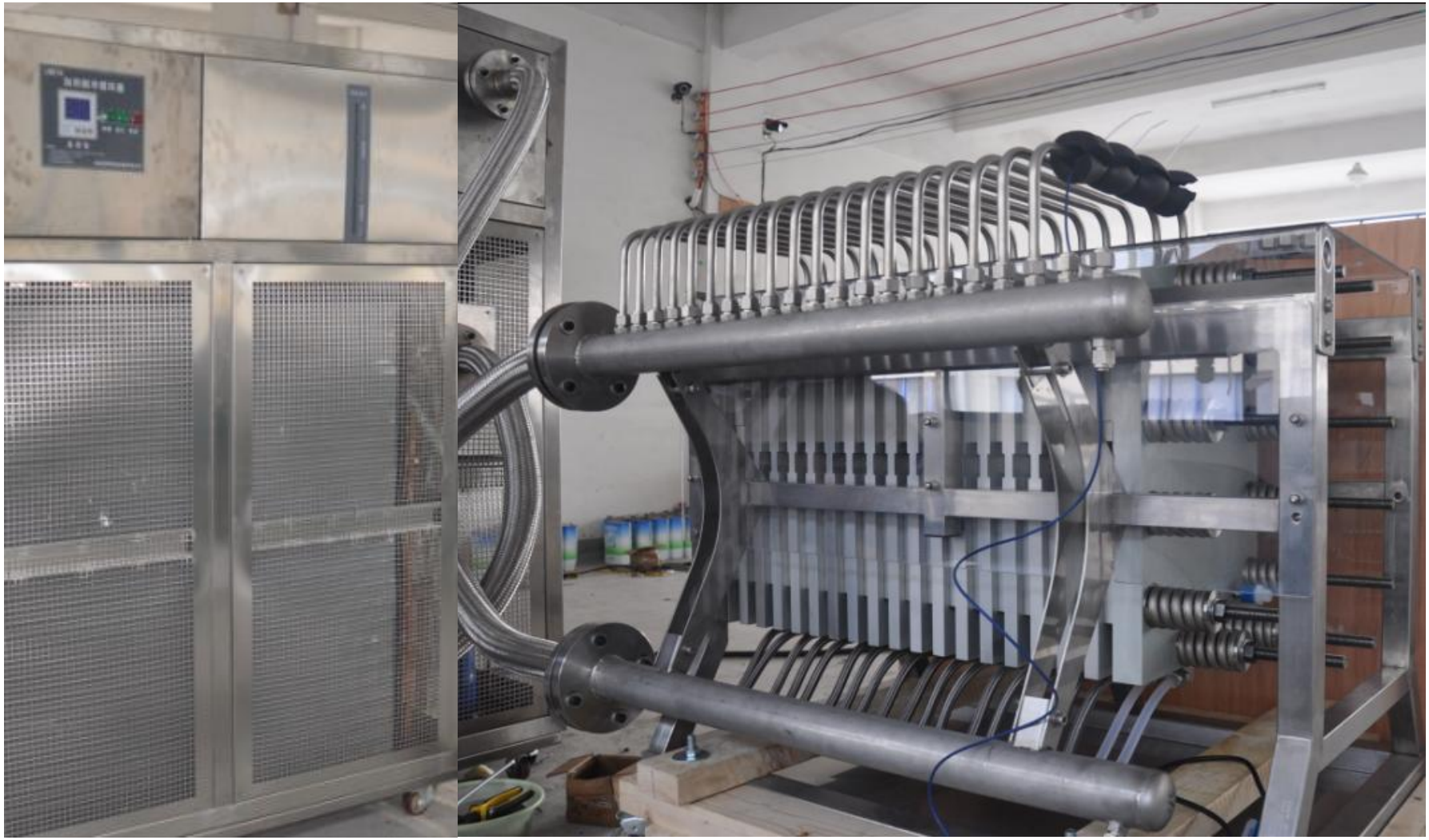


Seamless Scale-Up from G1 (80 t/y) to G3 (1000 t/y)

Installation in Shandong, China (2013)



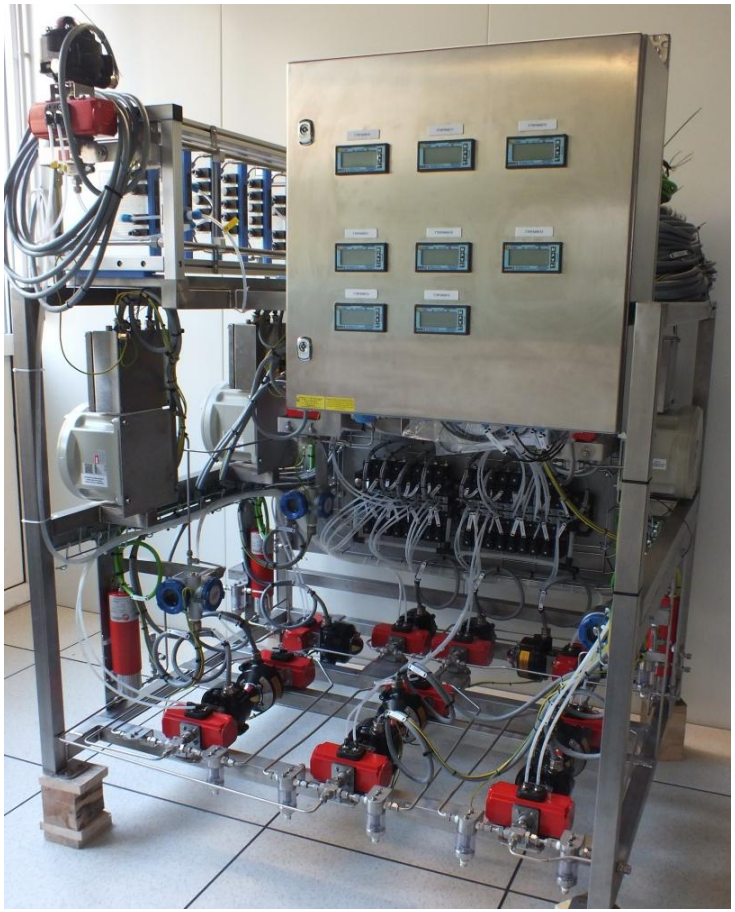
G4 SiC industrial installation in Jiangsu, China (2012)



More and more production cases in various chemistry fields

Fine Chemistry Production on G4

API Production on G1



Continuous production of fine chemicals is real : Seamless scale-up from G1 to G4

南京炼油厂有限责任公司

Seamless Scale up from G1 to G4 : Significantly changes equipment layout and safety management

- **Scaled flow up by >25 times from G1 to G4**
- **1st sample fully met product specs (2014.1)**
- **Same yield (99.8%) achieved in G1 and G4**
- **Manpower reduced 70%**

Angelini Pharma G4 reactor system for Active Pharmaceutical Ingredient (API) production

- Development done with a G1 SiC reactor
- Seamless scale-up to a G4 size reactor
- Installation of a G4 reactor with related dosing lines
- ATEX and FDA compliance requirement
- Timeline from first talk to chemistry running in G4: less than 2 years.

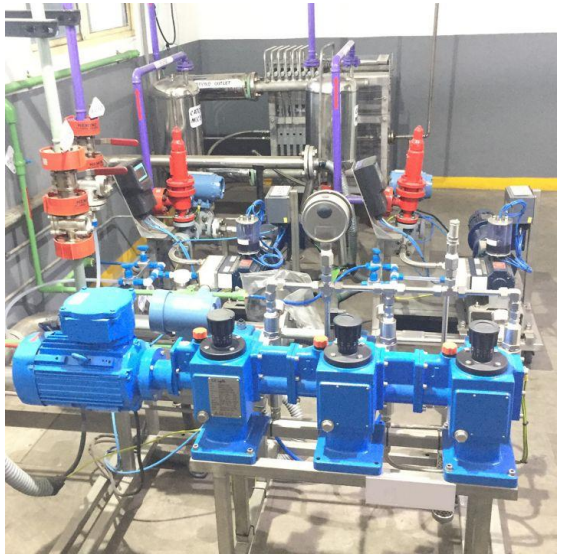
ANGELINI

**Pictures are a courtesy of Angelini (Italy)*

Anupam G4 reactor system for specialty chemistry production

ANUPAM RASAYAN INDIA LTD.

- Installation of a G4 reactor with related dosing lines
- Continuous manufacturing of products where difficult chemistries can be manufactured in a safer and more sustainable manner



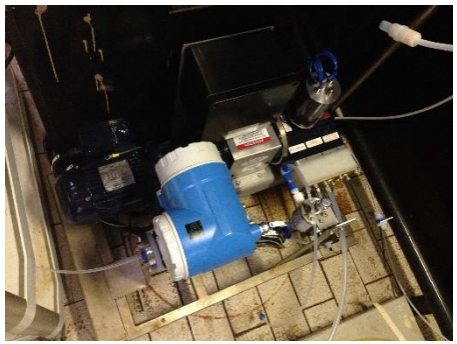
**Pictures are a courtesy of ARIL (India)*

From lab-scale to pilot/industrial-scale

G1 Corning reactor → G4 Corning reactor

Corning AFR seamless scale-up principle: Keep only residence time constant, assuming same mixing and heat exchange properties are provided by this technology





Test at pilot/industrial scale by using a G4 reactor:

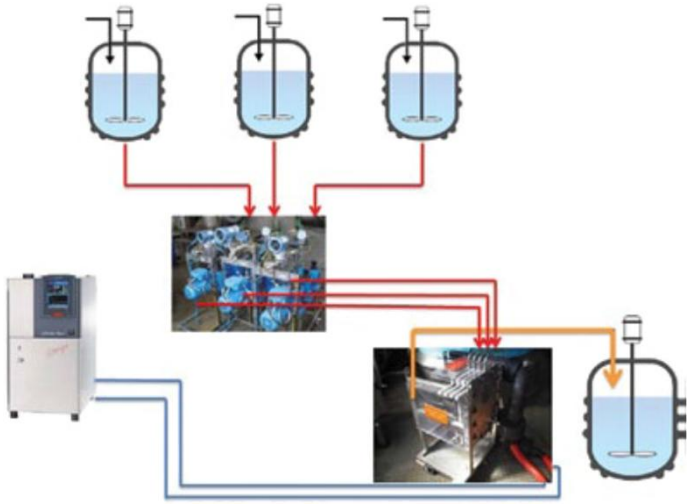
- 96% conversion at 25°C with a residence time of 82 seconds
- 8 plates of G4 reactor → achieve 1/3 of the industrial productivity

To achieve the required industrial production: add plates (ΔP < 18 bar) and numbering-up

LABORATOIRE LRGP REACTIONS ET GENIE DES PROCEDES

Multipurpose industrial flow system in a GMP and FDA inspected API manufacturing plant

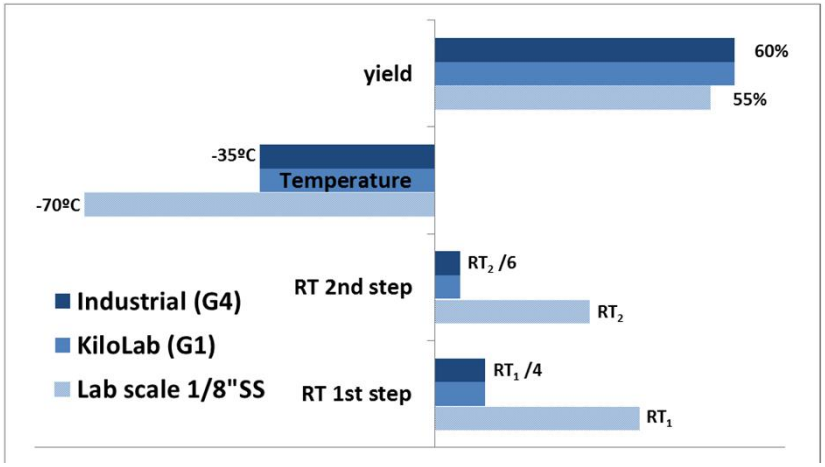
medichem



- 3 fully automated pumping units Atex compliant
- 1 industrial G4 Corning reactor (SiC)
- 1 Heating and cooling capacity from +200ºC to -60ºC

Outcome

- *Low temperature reaction not scalable in batch*
- *10 industrial batches of API intermediate produced*
- *Smooth and Quick scale-up from Kilo-lab to Industrial scale*
- *COGS savings of more than 30% vs external sourcing*



Production Plant Installations

Solutions for Green Continuous Manufacturing

Corning G4 reactor system with 2 dosing lines, 1 temperature zone control and DCS monitoring with a footprint of 15m²

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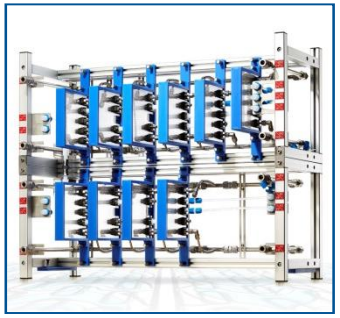
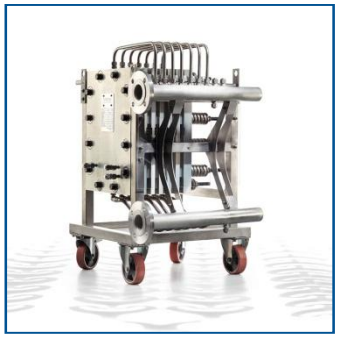




Selective Hydrogenation

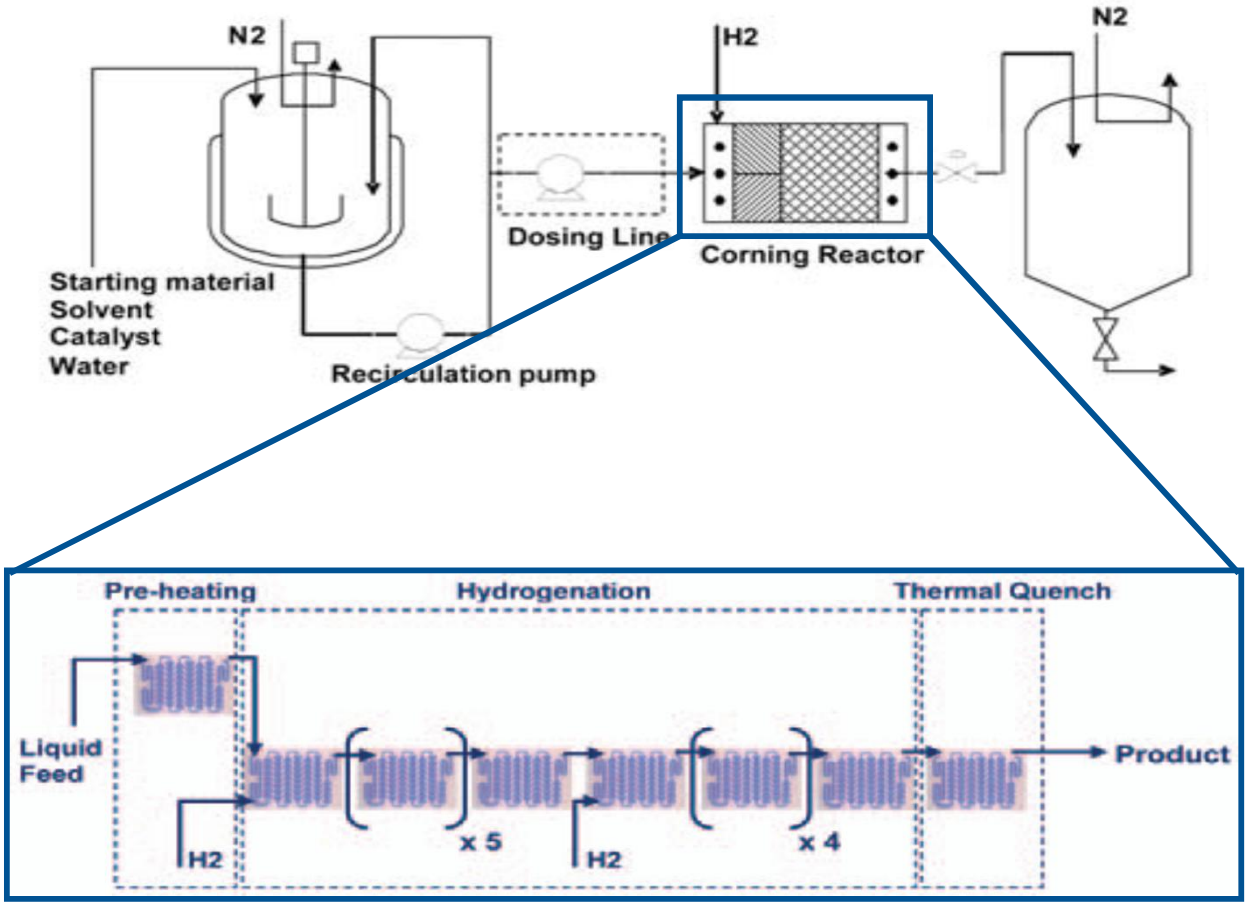
sanofi aventis
L'essentiel c'est la santé.
cpi ...the future inspired

Customer issues:

- Highly exothermic (>400 kJ/mol)
- Catalyst in slurry (30 µm)

Batch Process:

- Product 35% w/w
- 30°C
- 0.4% of catalyst



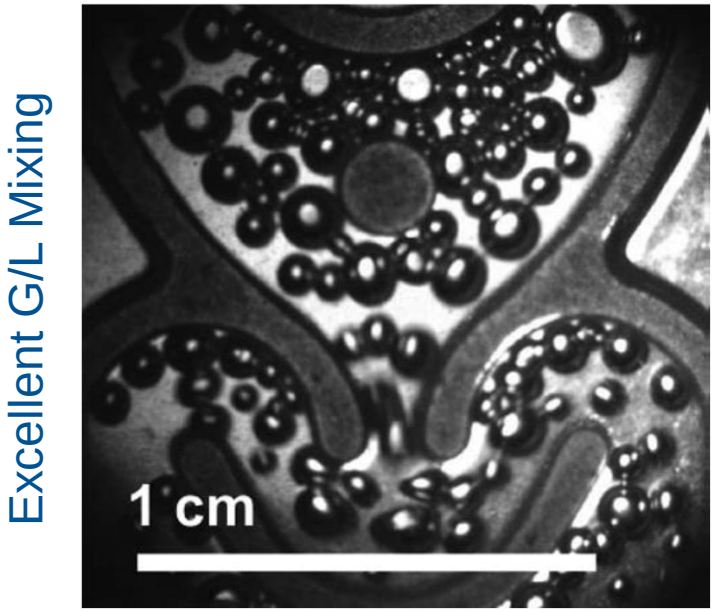
Reactor Size: G1

Ref: Chemistry Today • Vol 27 n 6 / November-December 2009

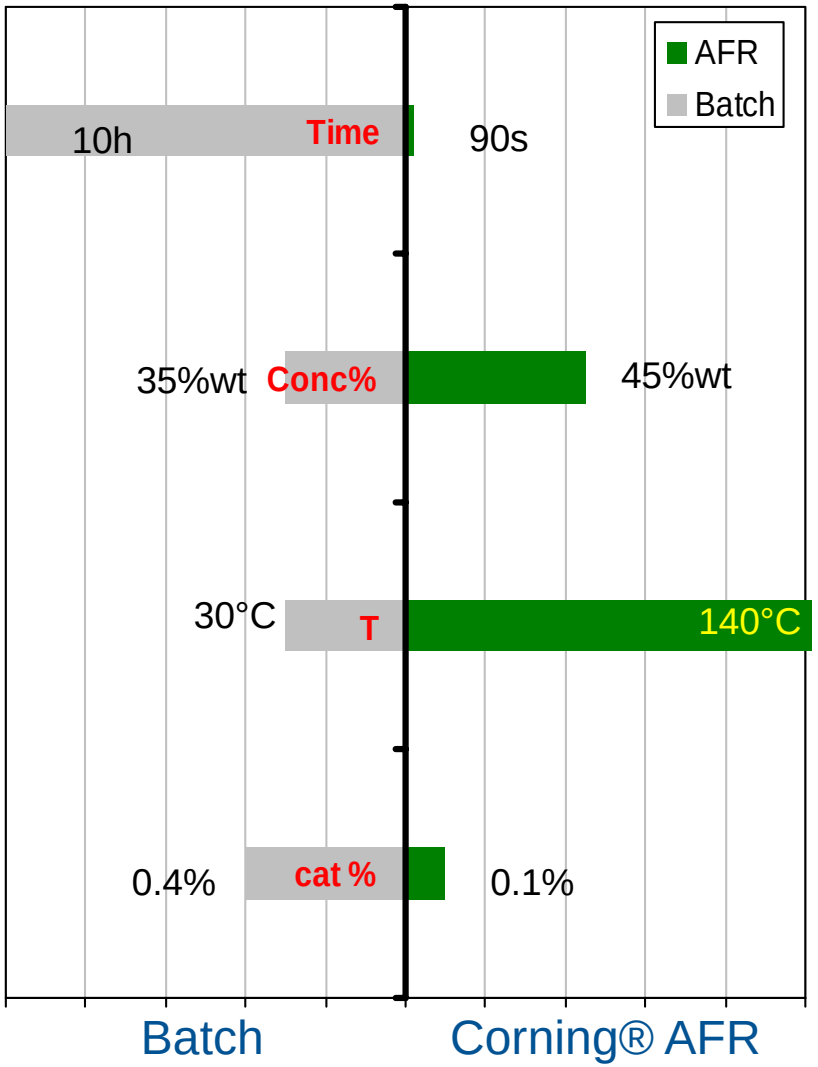
Selective Hydrogenation

Batch Process:

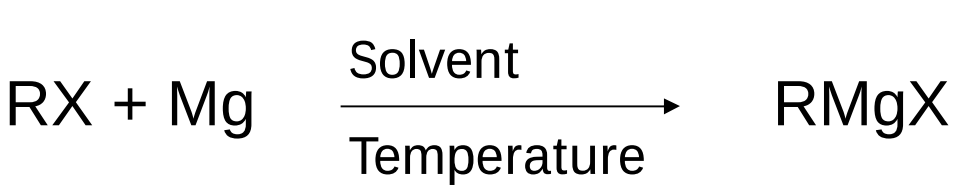
- significant catalyst reduction
- >98% conversion & selectivity
- Impurity profiles within specification

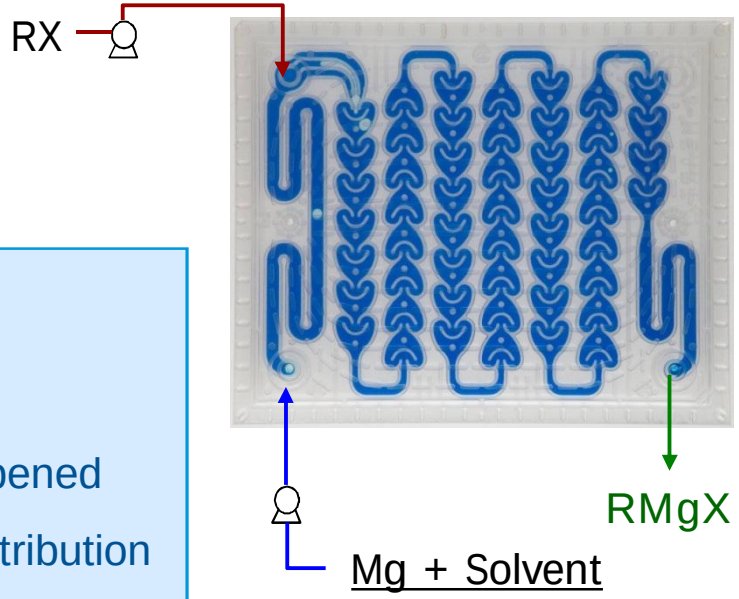


Excellent G/L Mixing



Grignard Reagent (RMgX) Preparation





Advantage from AFR technology:

- Superior heat transfer ensured uniform temperature
- Superior mixing between liquid and solid particle happened
- Plug-flow behavior leads to narrow residence time distribution
- Short & precise contact time

Reactor Size: G1

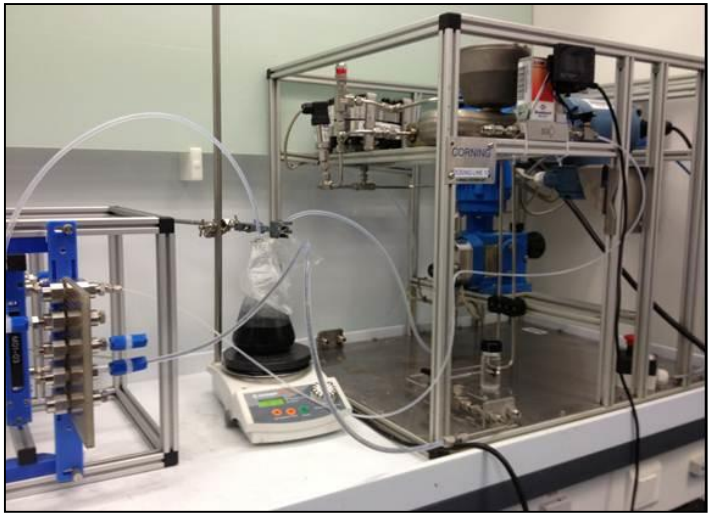
Results:

- Precise control leads to better purity of final products
- Better purity & solubility delivered for the final products comparing with “batch” process
- Generated Grignard reagents react with a variety of carbonyl derivatives

Particle Handling in Corning® AFR

- Corning Reactors can handle solids with a variety of particle sizes, solid types and loading.
- Enabling Solid/Liquid, Solid/Liquid/Gas application (e.g. heterogenous catalytic hydrogenation, diazo dye, etc.)

Slurry type	Particle size (μm)	Solid loading	Slurry Hydrodynamics
Pd/C	**30-50**	**2.5** g/L	**OK**
Silica beads	**63-200**	**2.5** g/L	**Ok**
Silica beads	**63-200**	**20** g/L	**OK**
Organics*	**<50**	**500** g/L	**OK**
Diazo*	**< 50**	**0,2** M	**OK**



**Based on typical values and experiments. Other conditions or products than tested should be validated by preliminary tests*

Continuous Cristallization

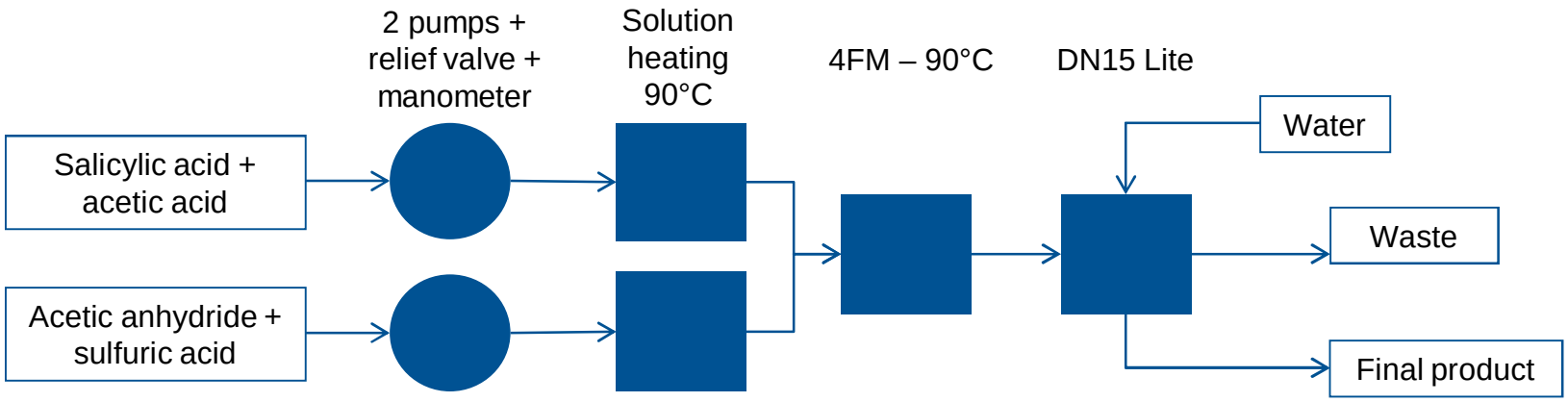
- NiTech – DN15 Lite
- COBR : Continuous Oscillatory Baffled reactor

- Pressure: max 2 bar
- Temperature: max 100°C
- Materials: Borosilicate glass and PTFE

- 3 thermostats
- 1 peristaltic pump

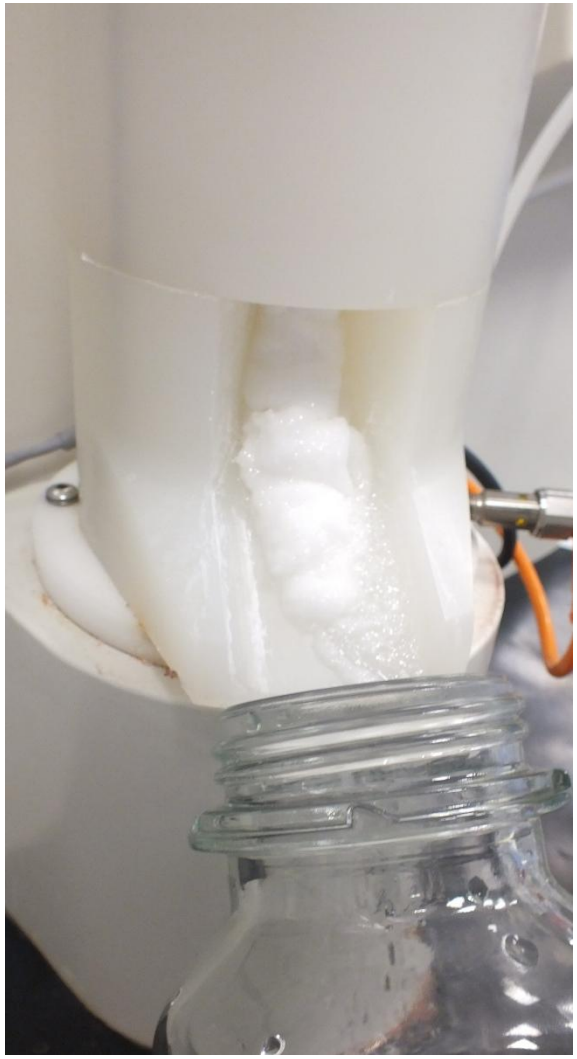
Continuous Cristallization

- Reactor G1 6FM



- Final Parameters
  - Total G1 flow of 20 ml/min
  - Water flow of 30ml/min
  - Temperature gradient 50°C/30°C/15°C (2/3/3 tubes)
  - Frequency 1.5 Hz, amplitude 35mm
- Full conversion and cristallisation yield 60% (not optimized)

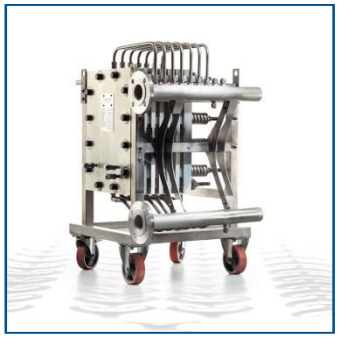
Continuous Cristallization



Continuous Cristallization

Presentation Outline

1. Introduction
2. Seamless Scale-Up
3. Industrial Examples
4. The Challenge of Solid handling
5. **Outlook**

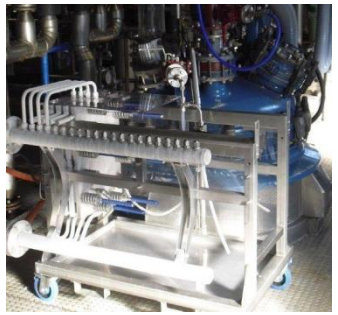


Concluding Remarks

- **Corning Advanced-Flow Reactors provide**
  - High Mass transfer
  - High Volumetric Heat transfer
  - Seamless Scale-up

- **Corning Advanced-Flow Reactors deliver**
  - High performance reactors
  - Turn key solution with the required auxiliaries
  - Customised solution to fit individual needs

- **Corning Advanced-Flow Reactors offer**
  - Dedicated support to customers all over the world
  - Technical data obtained by a dedicated R&D team
  - Solutions for customers to move faster to production



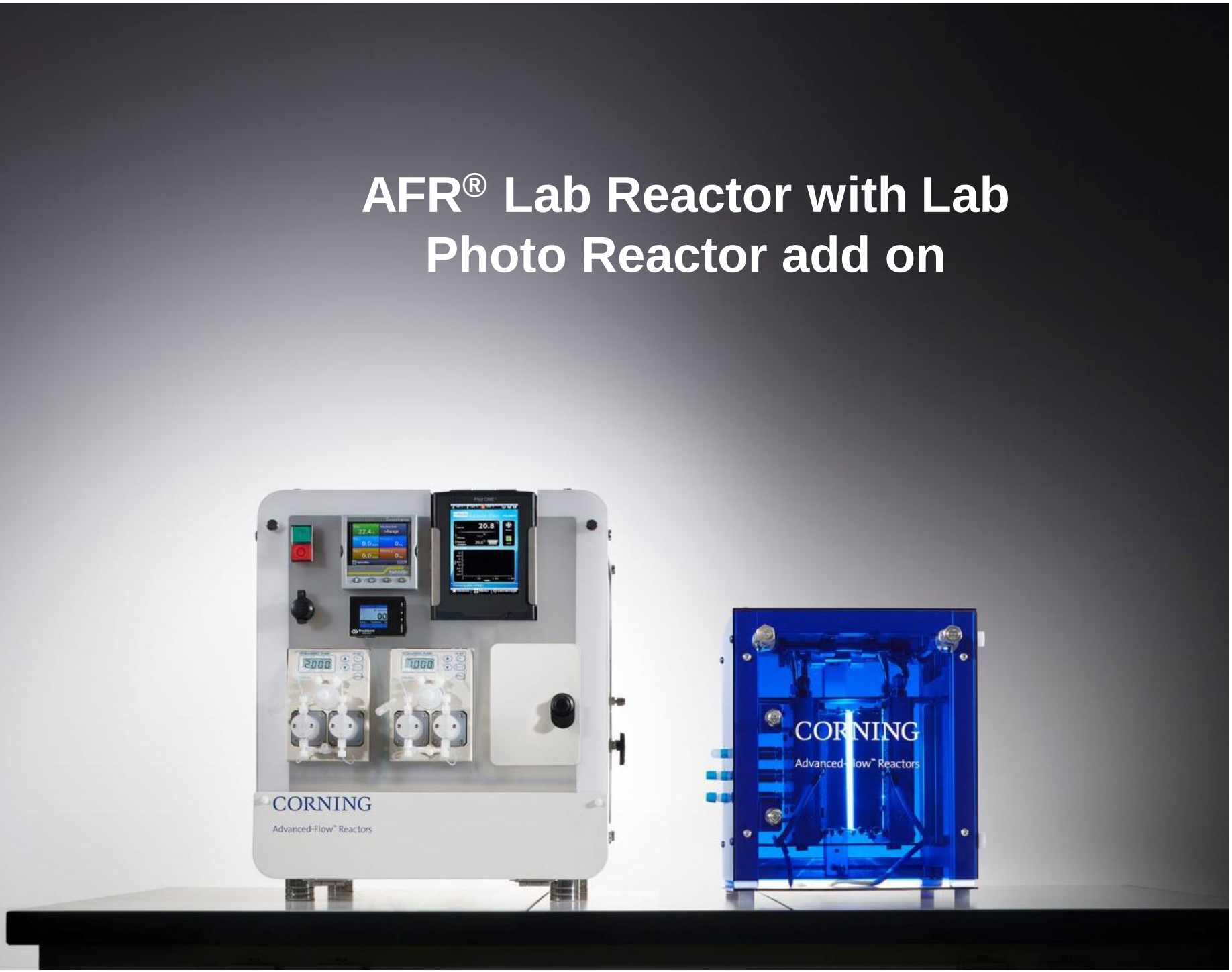
What is new? The AFR® Lab Reactor

A complete Plug and Play Lab System
(reactor + auxiliaries)

Ready to start & easy to use

Being seamless scalable with AFR® products

AFR® Lab Reactor with Lab Photo Reactor add on



Thank you for your attention

Questions ?

Advanced-Flow™ Reactor Technologies

www.corning.com/reactors