CONTINUOUS API MANUFACTURE

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Chief Reactor Engineer
CORNING SAS
October 16-17, 2013

Outline

- Introduction to Corning
- Continuous flow and process understanding
- Continuous flow and process control
- Continuous flow and material certification
- A case of industrial production of API in flow
- Conclusion

Corning is the world leader in specialty glass and ceramics

Founded in 1851Founded in 1851

Headquartered in Corning, NY

Global operations

Over 24,000 employees

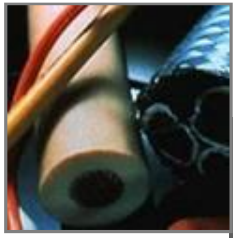
Fortune 500 Rank (2012): 328

$8 billion sales (2012)

~ 10% of annual sales to R&D

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

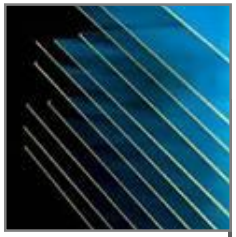
1879
Glass for Edison's light bulb



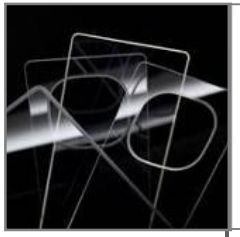
1934
Dow Corning silicones

1952
Glass ceramics

1970
Low-loss optical fiber



1982
LCD glass

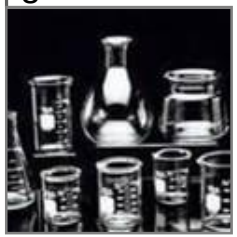


2007
Thin, lightweight, cover glass

Ultra bendable fiber

Pre-1900	1910	1920	1930	1940	1950	1960	1970	1980	1990	2000	2010

1915
Heat-resistant Pyrex® glass



1947
TV tube mass production

1972
Substrates for catalytic converters

2002
Fluidic module AFR*

2010
Thin-film photovoltaic glass

* Advanced-Flow™ Reactors

Corning Gorilla Glass®

History of Corning Reactor Technologies: One decade of expertise

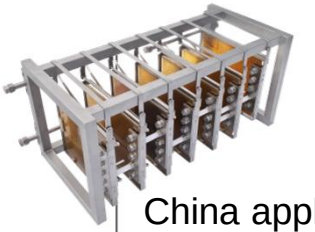
Concept development
Customer collaborations

G1 reactor

G2 reactor
Bank concept

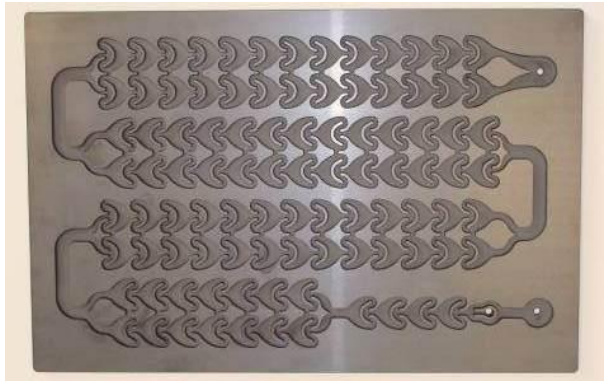
MIT
collaboration

G3 Glass reactor



China applications lab
India Sales Office

2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012



Collaborations with
platforms in Europe

European
applications lab

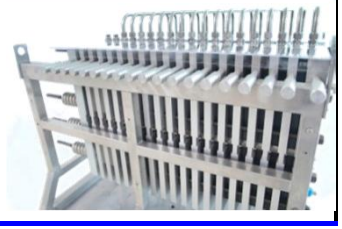
Low Flow
lab system

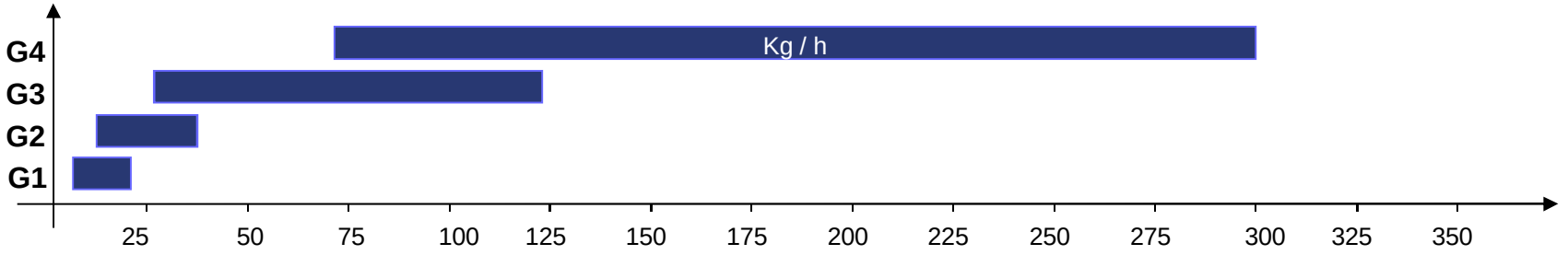
G4
Ceramic reactor

Continuous flow reactors production range

Low Flow	G1	G2	G3	G4
0.45 ml	8 – 11 ml	21 – 25 ml	55 – 65 ml	200 – 260 ml
T° -60 to 200°C, P° up to 18 bar, metal-free reaction path				





Seamless Scale-up

Quality By Design and Continuous Flow Reactor

ICH Q8 (R2) emphasizes " Product and Process understanding and process Control"

Was the wording "know –How" invented for the chemist?

We will focus particularly on API manufacturing and control

What makes a chemical process easier to understand and to monitor in continuous flow reactor rather than in a batch reactor?

Process understanding

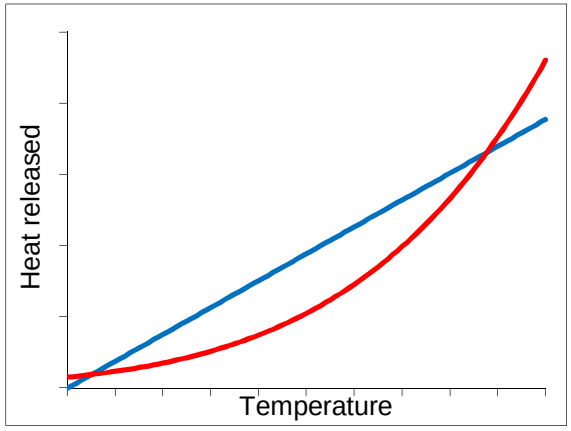
What are the requirements of the chemistry?
chemical reaction needs ⟷ chemical engineering capabilities of the equipment

Which parameters in the Chemical Process will influence the quality of the product, and to which extend (PAR, DS…)

How to predict in advance the influence of the size of the production equipment?

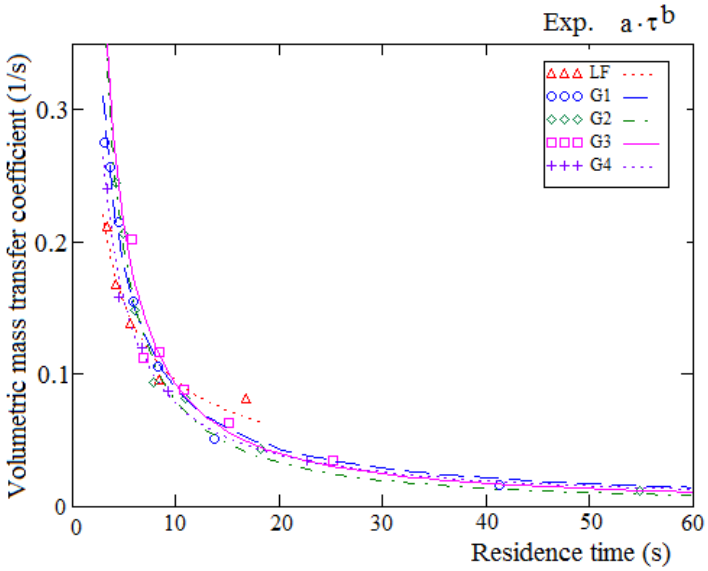
Chemical reaction's need

Chemist need	Chemical engineering requirement
Contact between the molecules of the reactants	**MIXING / MASS TRANSFER**
Keep the molecules in contact during a sufficient time to allow the completion of the reaction	**RT**
Does not keep the molecules to many time in contact to avoid side reactions	**RTD**
Isothermal condition / reaction enthalpy release	**HEAT TRANSFER**



What is the limiting factor: mass transfer or the kinetic of the reaction?

A nice tool for limiting factor assessment



In Continuous flow reactor, most generally Mass transfer efficiency is directly linked to flow rate, and therefore easy to monitor

	Organic phase	water phase	gas phase	temperature	inlet pressure	reactor volume	Apparent RT
	ml/mn	ml/mn	sl/mn	°C	bar	ml	s
Run187	18	15,5	0,700	100,00	14,00	48,00	86,0
Run53	36	29	1,400	100,00	14,00	96,00	88,6

Product	Impurity 1	Impurity 2	Impurity 3
% area	% area	% area	% area
81,9	8,6	0,5	1,2
91,2	5,5	0,7	0,5

Better knowledge of the process at lab scale with continuous flow

Dynamic and quick response

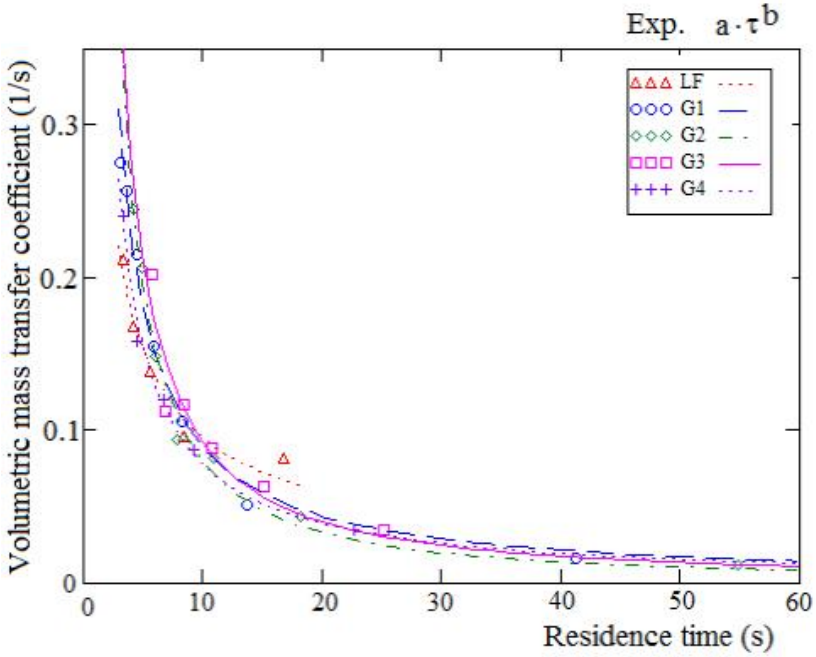
Plug flow behavior

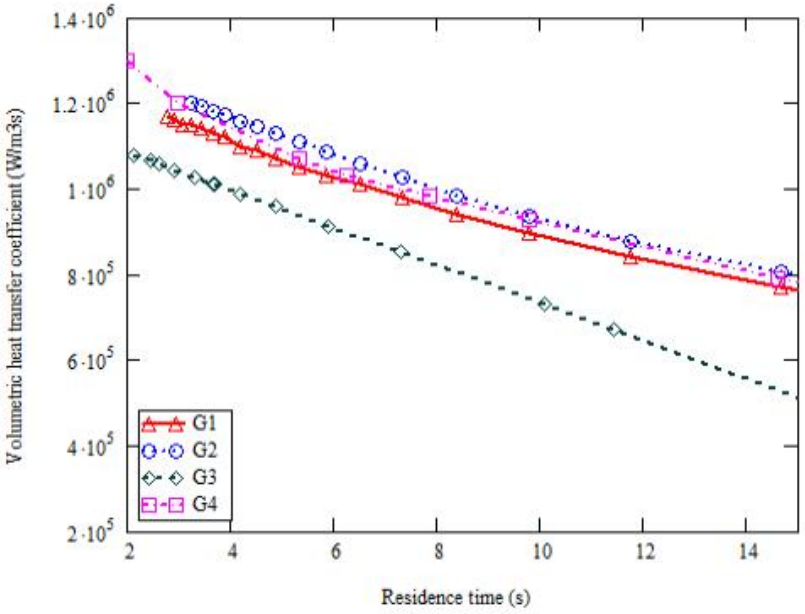
Impressive number of steady state conditions in 8 hours.

The limitation is the analytical capability, not the continuous flow reactor delivery

That can be directly extrapolated to production

Corning AFR reactors keep the chemical engineering reactor properties at the same value over all range, allowing a “seamless” scale-up from lab to production.





Reactor capabilities versus reaction's need

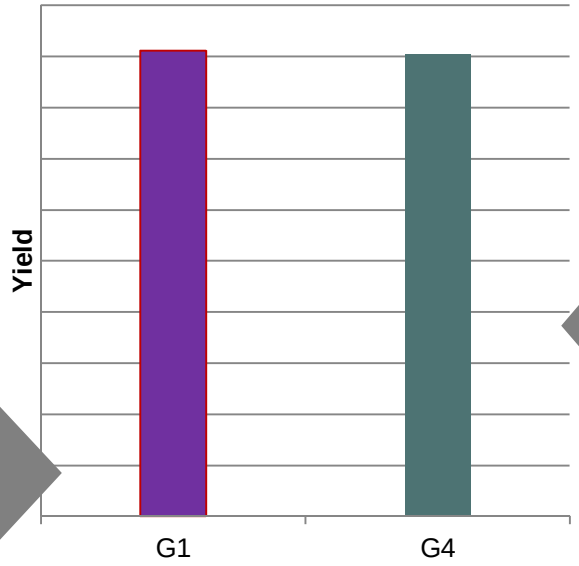
If the reactor capabilities will be kept at the same level for all sizes, then the chemical needs will be satisfied at the same level, the output will then remain constant.

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

Actual scale-up from Lab to Pilot

Multiphase application: L/L/G

Lab G1
80t/y



Production, G4
2000 t/y

Which positive effect for an API development?

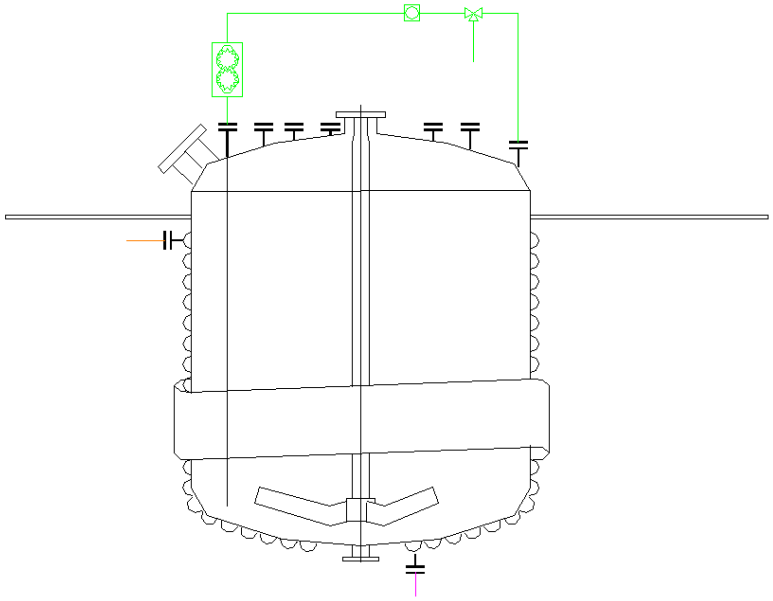
The process optimization made in lab at small scale, with few product, can be used directly in the production reactor

The PAR study can therefore be made at small scale and directly used for production as well, leading to time and material saving.

Process Control

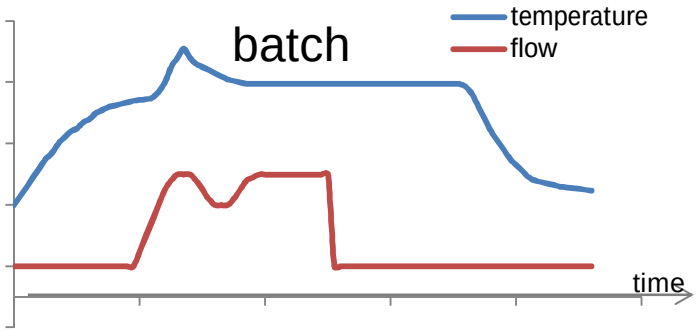
A prerequisite to control the process is to understand it (or at least to have a reliable and representative model –"black box")

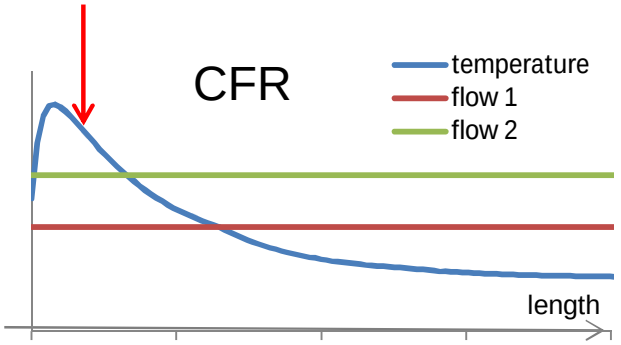
Are on line measurement easier in continuous flow than in batch?



Steady state and low inertia make the difference!

In steady state in a continuous flow reactor, time is no more a dimension





Any change in a parameter will be directly linked to a change in the process, not to the time anymore.

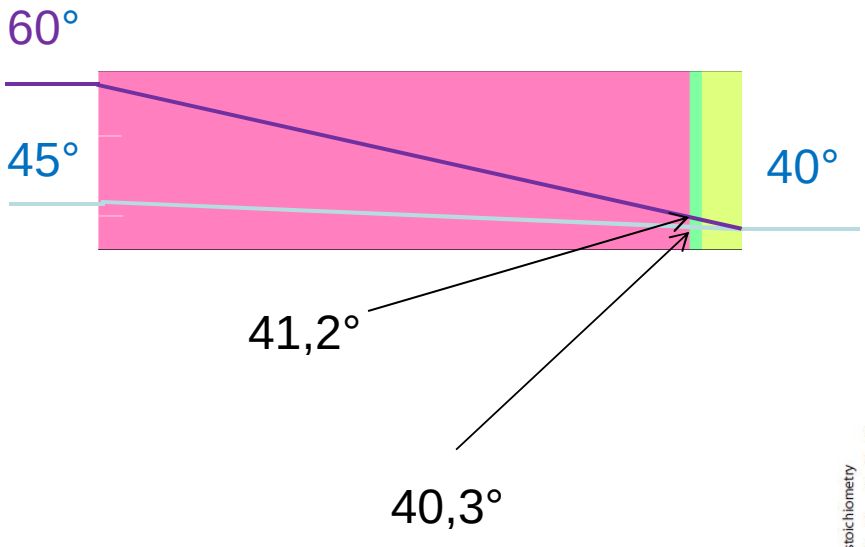
Therefore, the information has much more value.

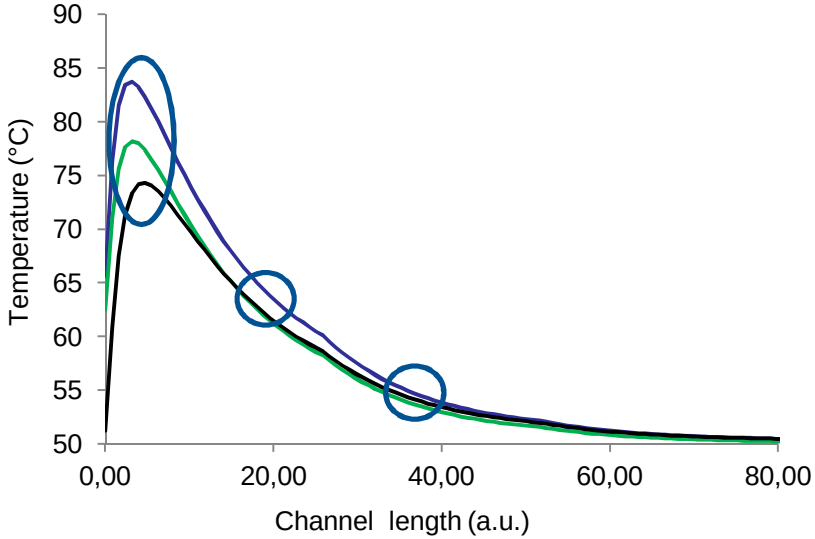
Low thermal inertia, and plug flow behavior give a quicker response to any change, and make corrective action quicker and more efficient

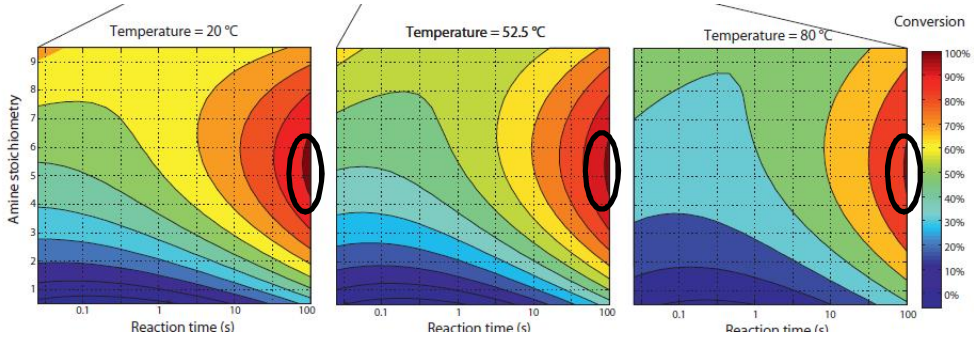
	weight (kg)	volume (l)
batch	8000	5000
continuous flow	500	5
ratio	26	1000

Which parameters to measure?

Process Temperature?







Access Flow. Application note N°1

Flow

Pressure

On line product analysis: An example of industrial case study

Organic Acid Chloride $\xrightarrow[\text{Toluene}]{\text{pyridine}}$ Organic Carbonate + Dimer

Partners: FDA:

CORNING:

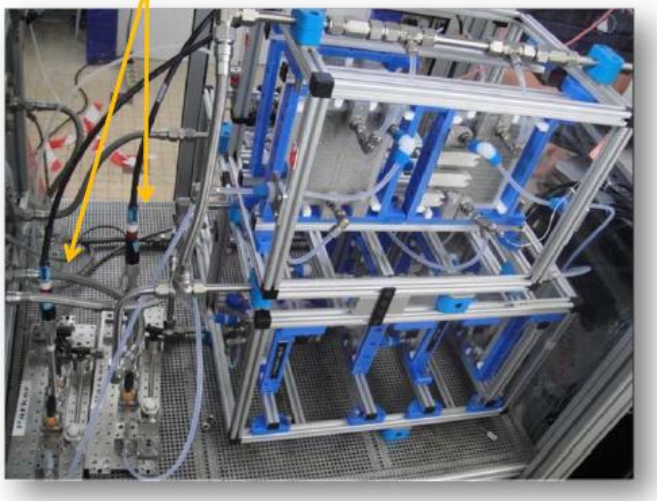
Kaiser Optical System
(Raman RXN2™ Analyser)

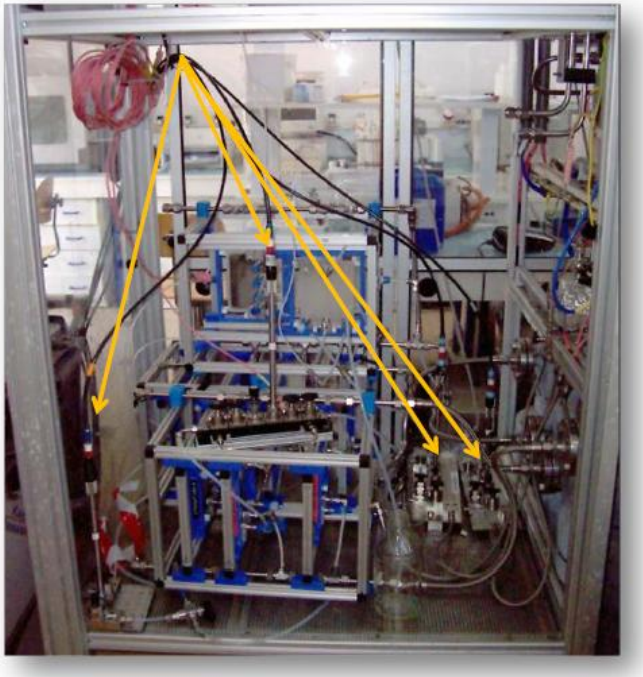
Parker (NeSSi sampling system):

Reactor lay out

Advanced Flow Reactor Images

Raman Probes



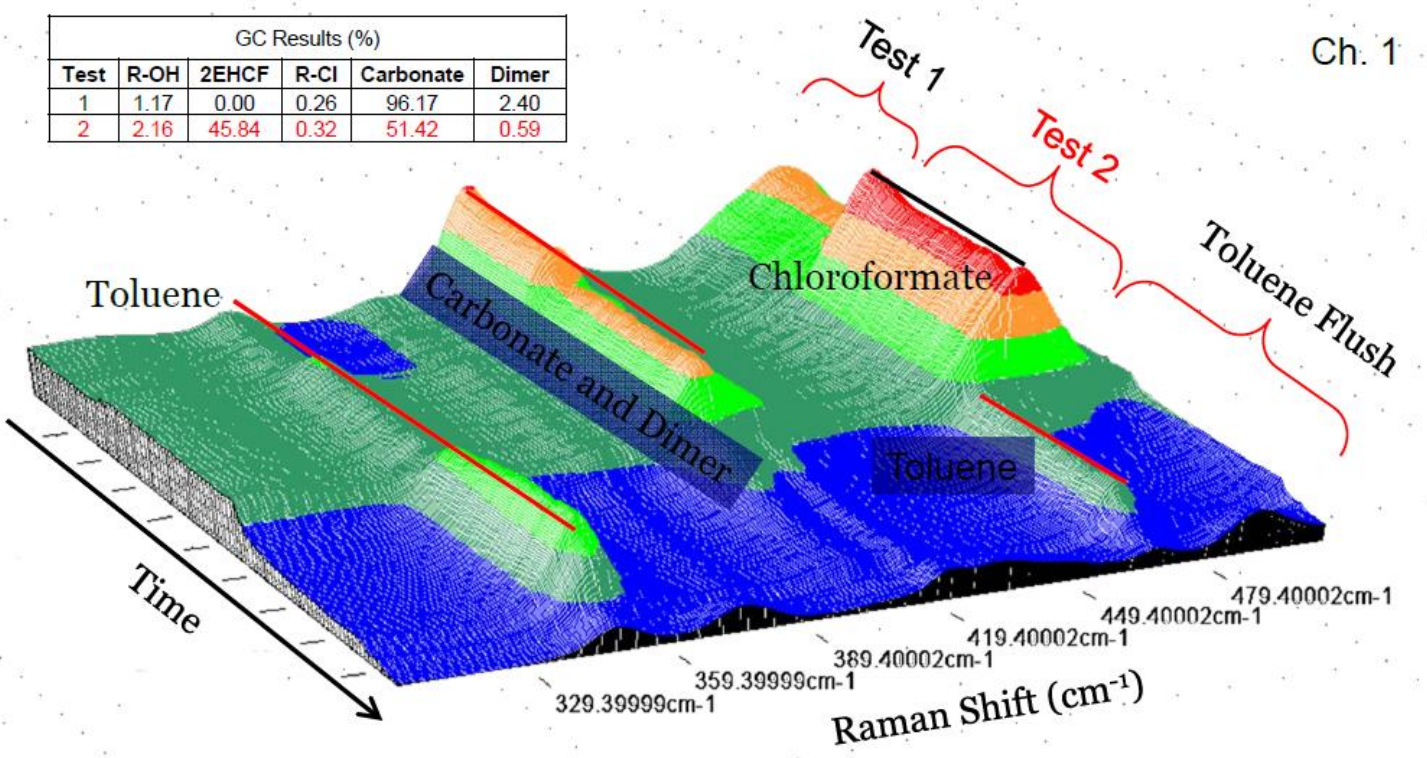


IMTeC 2010
Brian Marquardt
CPAC

Raman shift spectrum

3D Plot of Raman Reaction Data

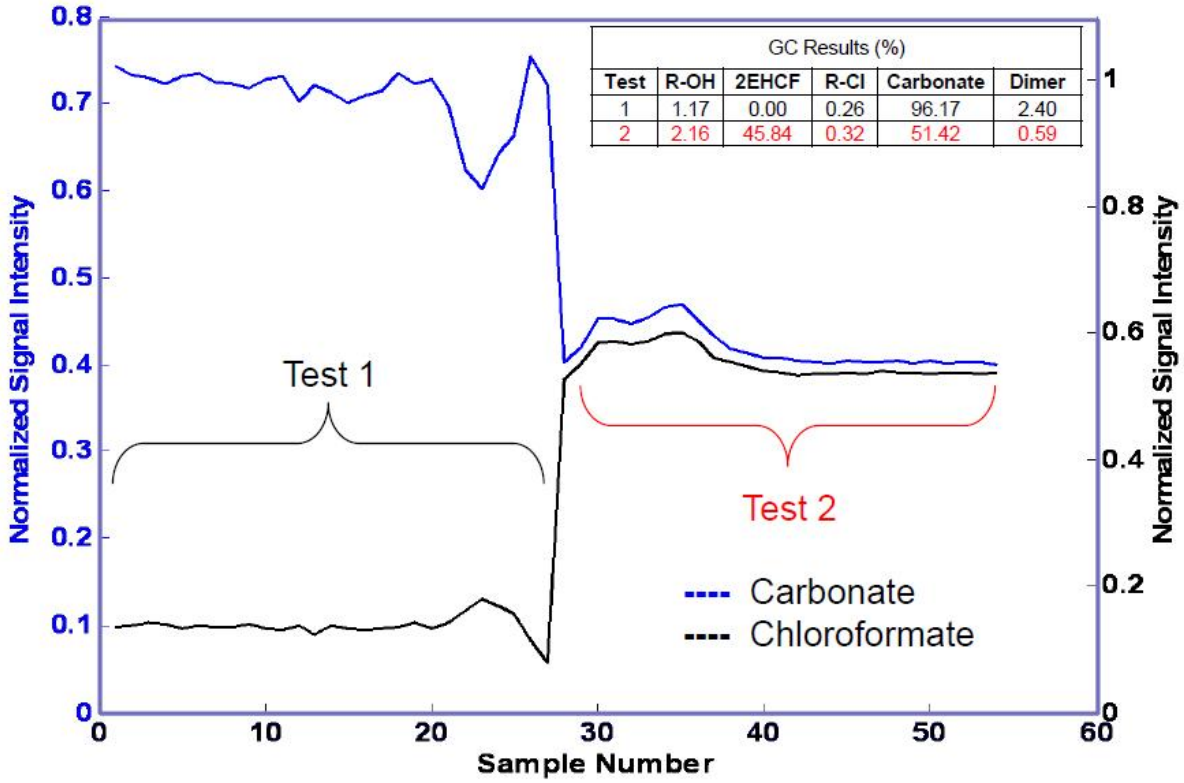
GC Results (%)					
Test	R-OH	2EHCF	R-Cl	Carbonate	Dimer
1	1.17	0.00	0.26	96.17	2.40
2	2.16	45.84	0.32	51.42	0.59



IMTeC 2010
Brian Marquardt
CPAC

Method calibration

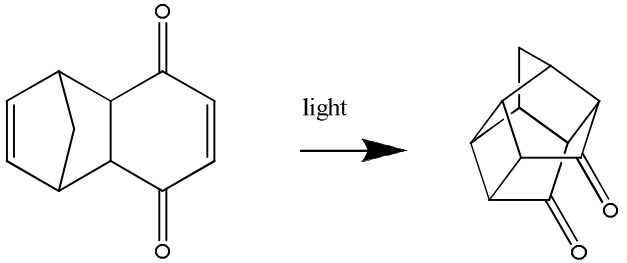
Reaction Profiles for 2 DoE Steps

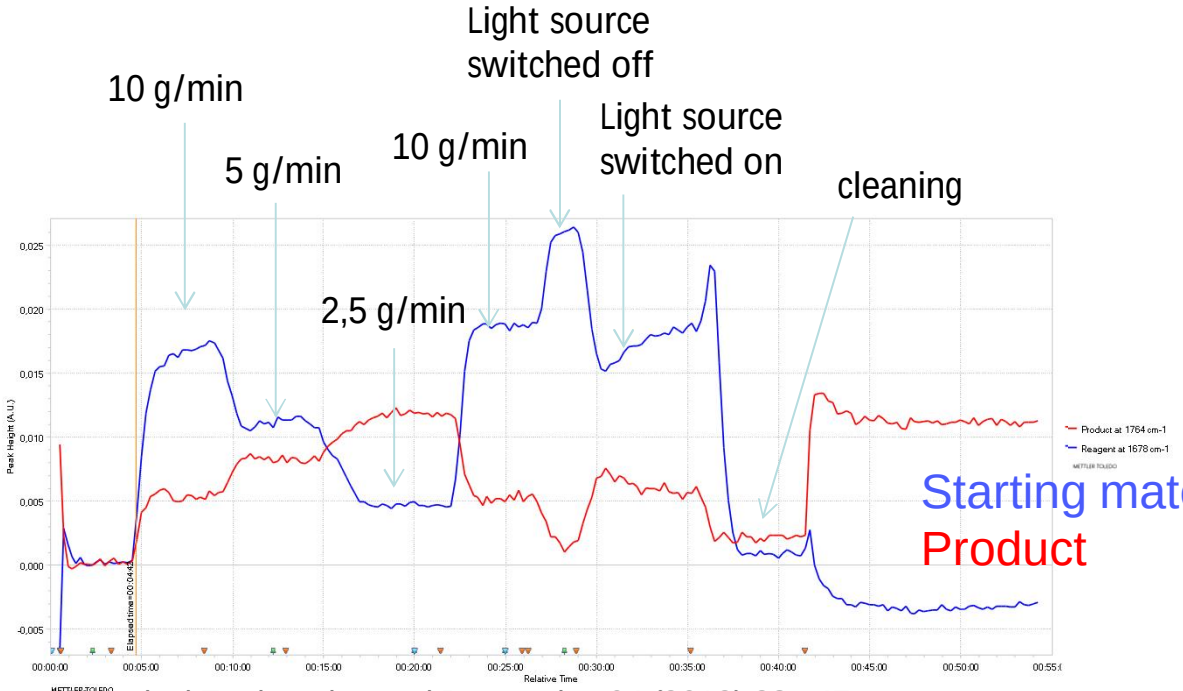


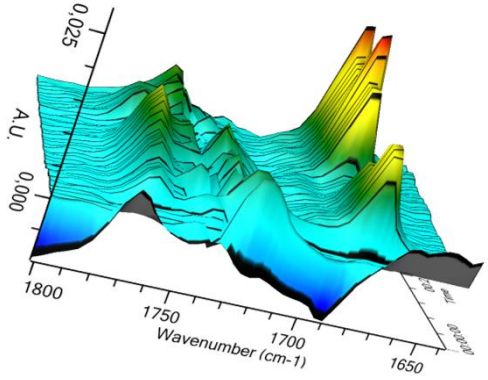
IMTeC 2010
Brian Marquardt
CPAC

On line product Analysis in day to day work: photochemisry coupled with IR on line.

- Corning PhotoReactor
  - Intramolecular 2+2 photocycloaddition*
  - Corning AFR combined with light source
  - Dominant emission line at 360 nm
  - On-line Infrared Spectroscopy







Starting material
Product

Mettler Toledo
Read IR™15

*Chemical Engineering and Processing 64 (2013) 38– 47

On line analysis: current limitation

On line analysis is not an universal tool.

Several technology are available in the market (IR, Raman, mass spectrometry…)

In any case, the utilization is not straightforward, a method has to be developed and validated.

The material of construction may be an issue for some cases (if metal free is required for corrosion issue…).

Response time?

Material certification

Industrial continuous flow reactors are industrial equipment, manufactured according to codes and standard of quality and traceability.

All metal parts used are delivered with 3.1 certificate

SiC has been validated according FDA compliance policy guides 7171.06 (2005) and 7171.07 (2005)

Perfluoro elastomer gaskets are purchased with certificate of compliance with 21, CFR, part 177.1550

The choice of auxiliaries (pumps…) has been made with the support of Corning experience in pumps selection


ZERTIFIKAT ◆ CERTIFICATE ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

CERTIFICATE

The Certification Body of
TÜV SÜD Industrie Service GmbH,
a Notified Body of the Pressure Equipment Directive (PED),

certifies that

CORNING

CORNING SAS
7 bis, Avenue de Valvins
F-77920 Samois sur Seine
France

implemented, operates and maintains a quality assurance system as described in the PED (97/23/EC) Annex III, Module D1

within the scope of

Manufacturing of
Corning ® Advanced-Flow™ G4 Ceramic Reactor.

The audit with the report number F-Q-025B-13 proves that the quality assurance system fulfils the PED requirements.

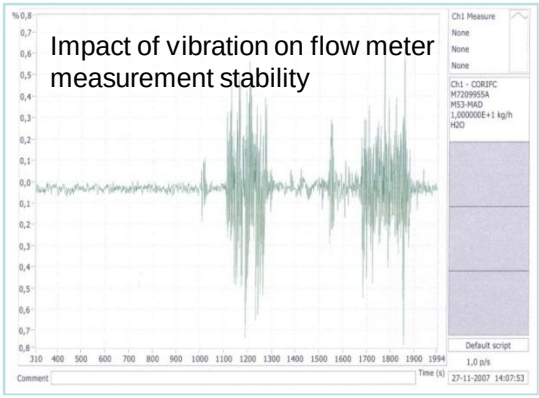
The manufacturer is authorized to provide the pressure equipment produced within the scope of the assessed quality assurance system with the following Notified Body number:

CE 0036

Certificate No.: DGR-0036-QS-1107-13

valid until March 22, 2016

Mannheim, March 26, 2013



How to clean a continuous flow reactor?

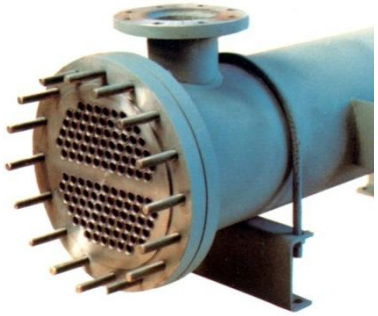
Cleaning of Continuous Flow reactor: poor answers

How to clean a batch reactor?

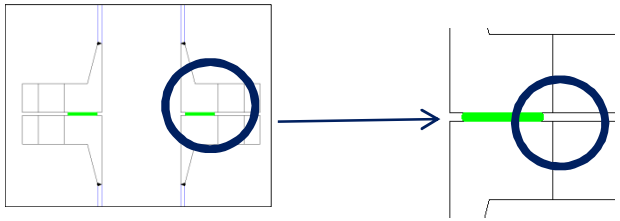
A 6 000 l glass lined reactor has an internal surface of 23 m².

Most generally, the reactor is fitted with a 24 m² exchanger (plus a 12 m² post condenser…)

Are the exchangers always open to check that they are clean?



What about singularities (gaskets, pump…)



Dead volume 1200 mm^3 for DN 50

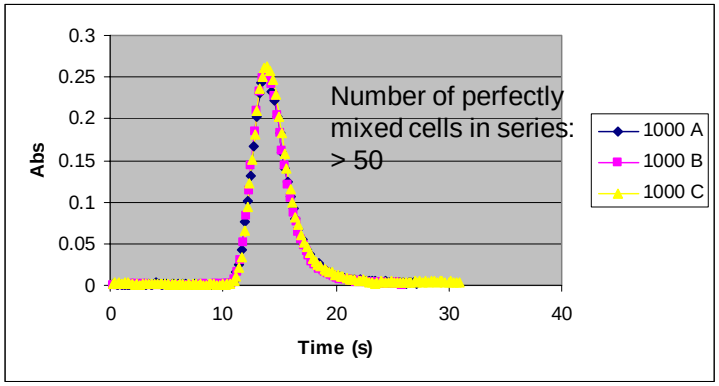
If you can clean a batch reactor, you will clean a continuous flow reactor as well

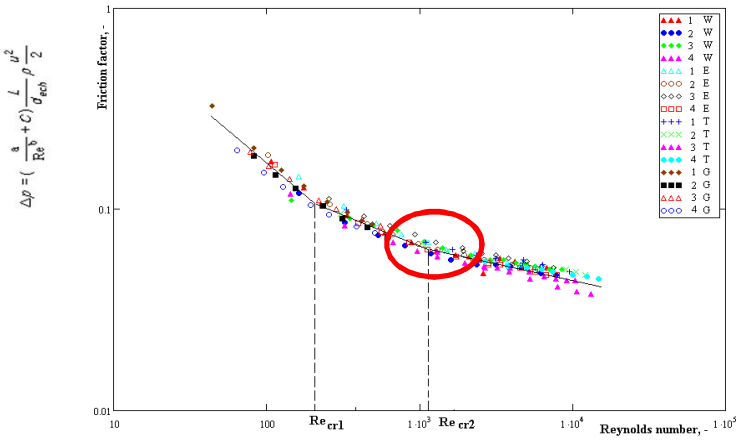
Cleaning of Continuous Flow reactor: better answers

The surface of glass or SiC reactor is very smooth (Ra <1 nm)

An AFR “equivalent “ to a 6 m3 GL reactor has a volume of 5 liter and a wetted surface of 3,5 m²

The flow can easily be turbulent with high mixing/ cleaning efficiency



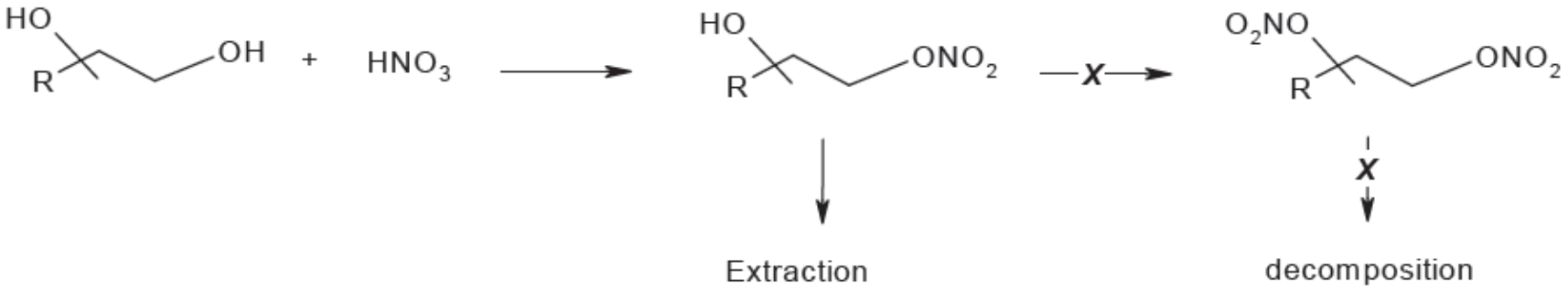


The flow is really a plug flow, which means virtually no dead zone.

Ultimately, drastic condition (dismounting and pyrolysis at high temperature) could be applied

The cleaning procedure and the demonstration if its efficiency is fully **part of the process** and has to be made at preliminary step

A case of industrial production of an API with AFR



Scale-up Conference, 2010

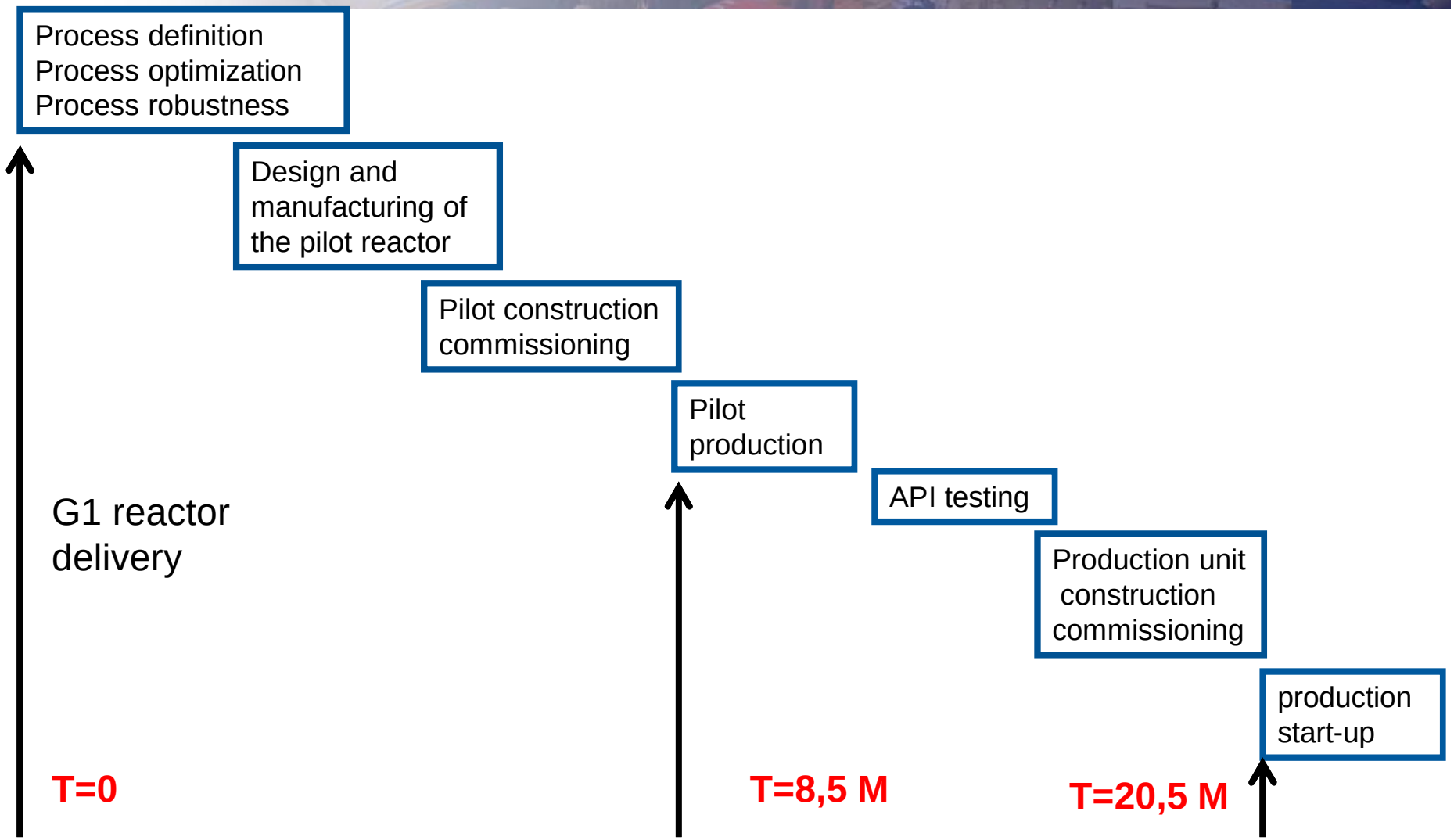
2nd symposium on Continuous Flow reactor Technology for Industrial Applications, Paris, sept 2010)

Moving forward step by step

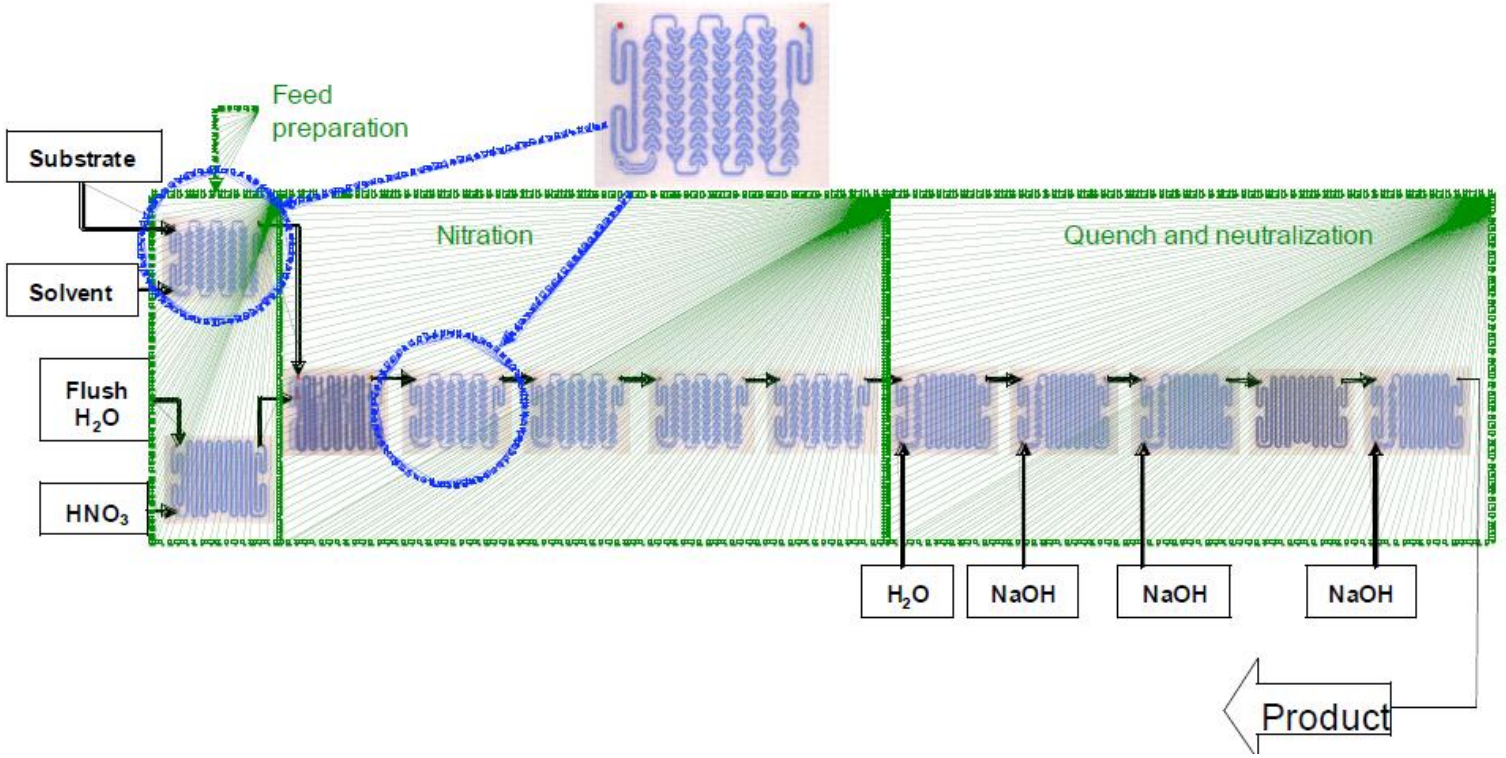
- Process definition, robustness and optimisation (G1)
- Production of several hundred kg for stage II by numbering-up (8 G1)
- PAR for production (G2 size)
- Production of several tons for stage III by numbering-up and scale-up (12 G2)

All pictures courtesy of DSM

In a very short timeframe



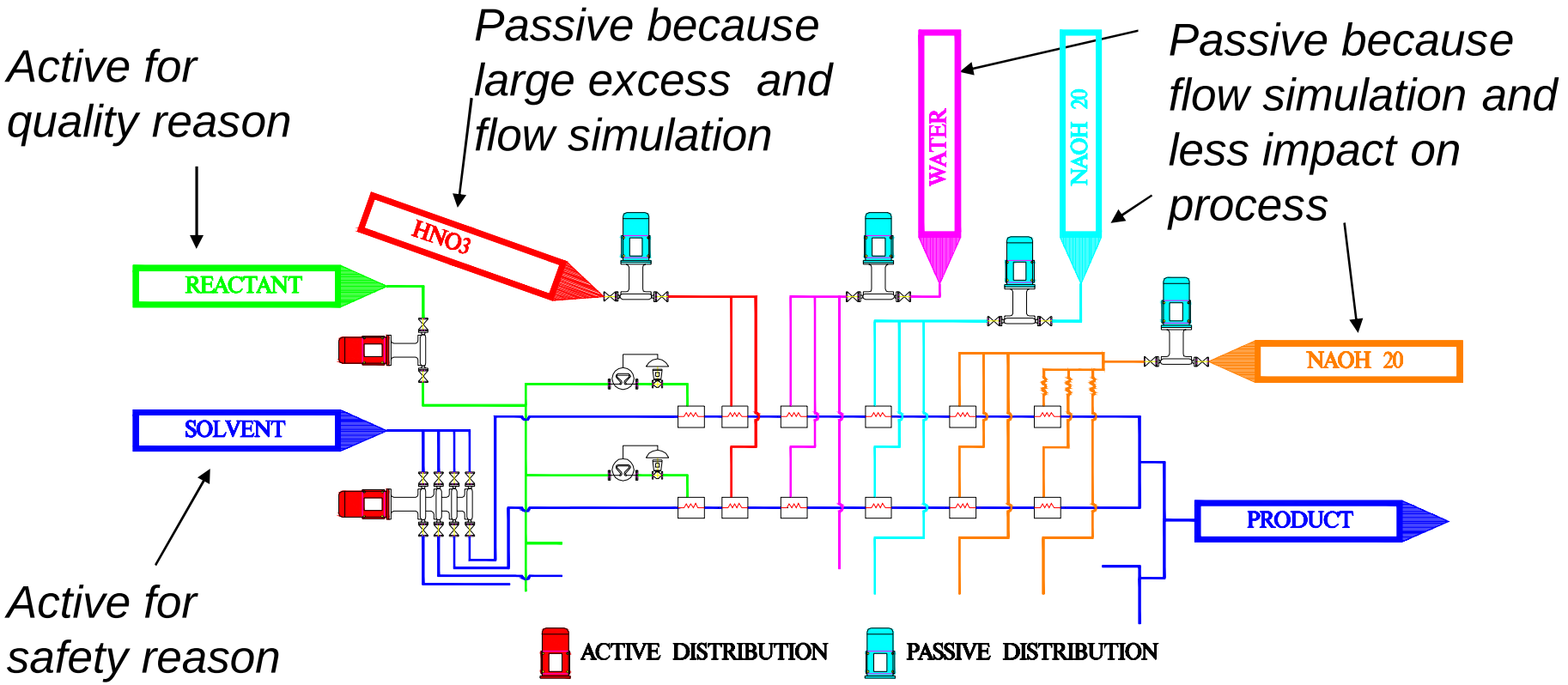
From lab to pilot: fluid distribution



7 feeds time 8 reactors = 56 feed inlet

56 single pumps or control loop is not realistic!

A flow control philosophy based on lab test and process robustness

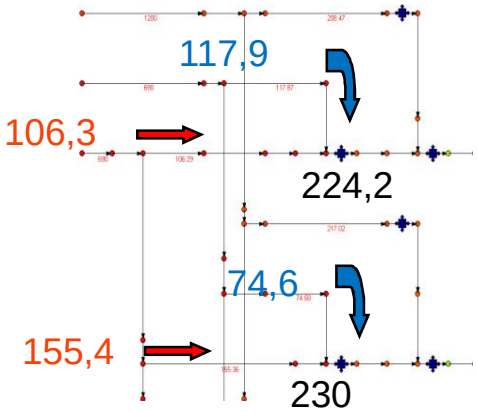


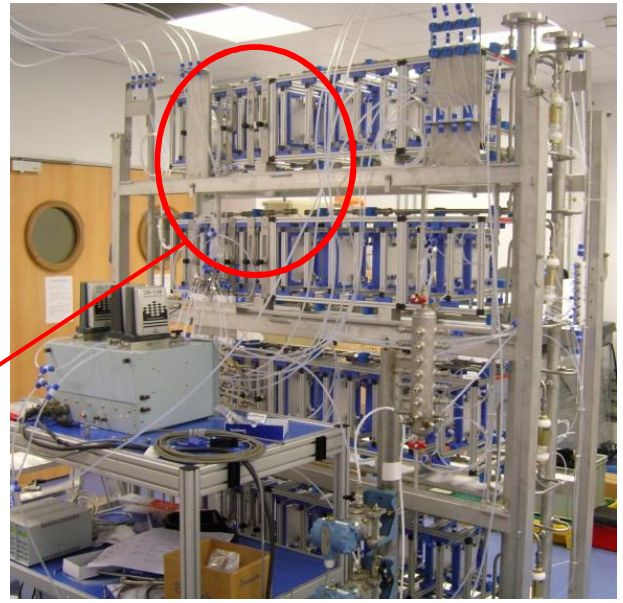
All flows are monitored (mass flow meter or ball flow meter)

The only temperature measurement were on utility side and at the reactor outlet

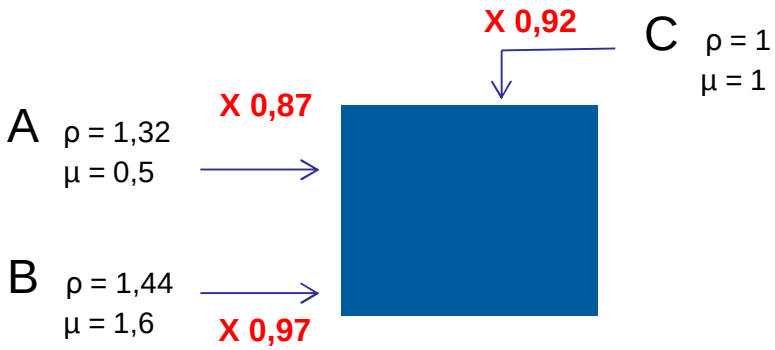
Validation of process control system

- Flow modeling

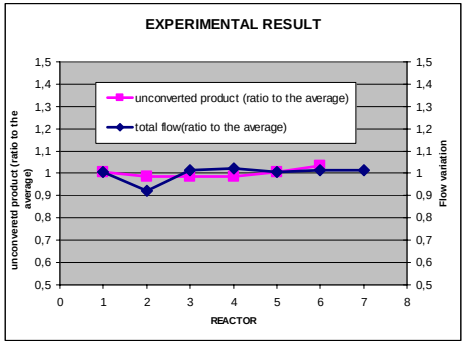


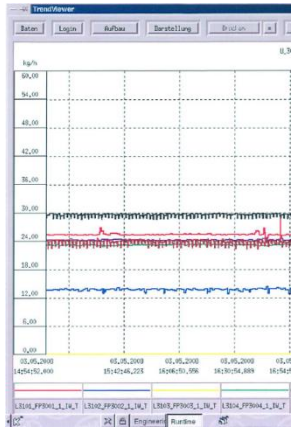


- Lab test and pilot water test



- Flow and quality monitoring during run of qualification





What would be the picture today?

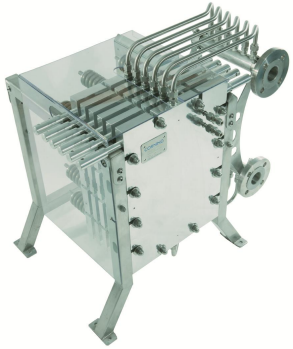
Lab test in G1

Lab test in G1

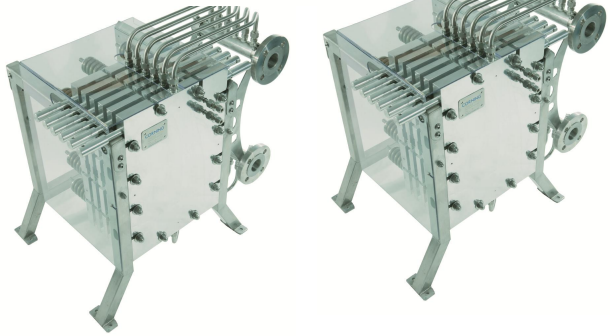
Pilot in 8 x G1

Pilot in G4

PAR in G2



Production in 12 x G2



Production in 2 x G4

Conclusion

Continuous flow bring significant advantages for the development and the production of API under c-GMP requirement.

The seamless scale-up of Corning® Advanced-Flow™ reactor allows to predict the behavior of the production reactor in the lab and the results of PAR study made in short scale can apply directly for production.

A good knowledge of the reaction mechanism is require to take full advantage of continuous flow, and to monitor closely the process.

Corning® Advanced-Flow™ reactor is an impressive tool for a better understanding of the chemical process.

Conclusion

The more you know about your chemical reaction, the better you can control it.

On line analysis is not directly linked with continuous flow, even it may be useful for a better control of the reaction

The good parameters to check in continuous flow are not necessarily the same as you use to control in batch.

The cleaning of the reactor is not unpredictable, it has to be seen as a part of the process, and study and optimized accordingly.

THANKS FOR YOUR ATTENTION

QUESTIONS?

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