L’innovation par les procédés

Christophe Gourdon, INP-ENSIACET, LGC Toulouse

Acte I : un contexte propice

"BUILD BACK GREENER"

"There is a lot that the medicines manufacturing industry should be doing, such as adopting technologies and approaches that lower the carbon footprint of the manufacturing supply chains."

"We need to attract global medicines manufacturing that deploy the latest innovations that are sustainable, highly productive, consistently high quality and are long term projects with job security".

Lord Bethell, UK Health Minister
18 Feb. 2021

"Continuous manufacturing could be the enabler for onshoring pharma manufacturing and helping to achieve Net Zero targets."

Johnathon Marshall, PwC
Feb. 2021

« Une relocalisation d'activités productives en France et en Europe sera d'abord la conséquence d'une évolution des politiques d'achats et des méthodes de production industrielle »

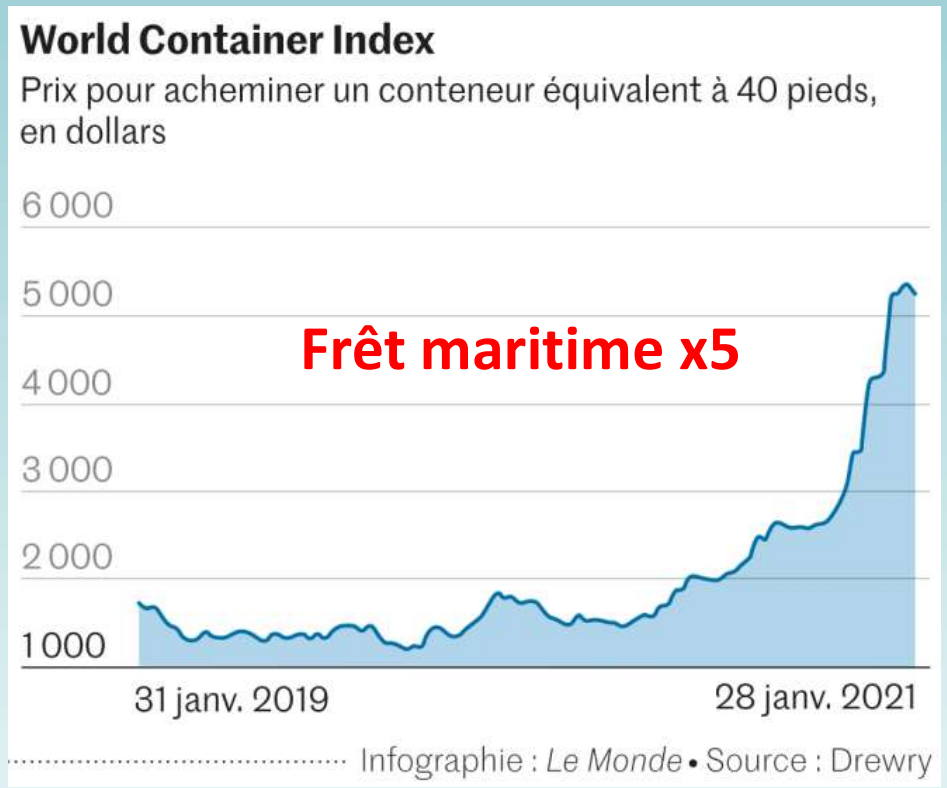
Extrait du Rapport PwC – CNA, Juillet 2020

Indice de criticité PwC

Contexte COVID-19 depuis 2019

« Aides à […] la production en Europe des médicaments anciens et à l'utilité démontrée, régulièrement touchés par des pénuries […]. »

Article UFC Que Choisir : Pénuries de médicaments - Les laboratoires et les pouvoirs publics - 10 Novembre 2020



Acte II : quoi de neuf en matière de procédés dans le secteur pharmaceutique ?

A long story of batch in fine-pharma sector …

- 50 years (before J.C.)

Fine-pharma facility, 2020

In « emerging » countries (India, China …):
the « flow chemistry » is emerging

Rotating Packed Bed

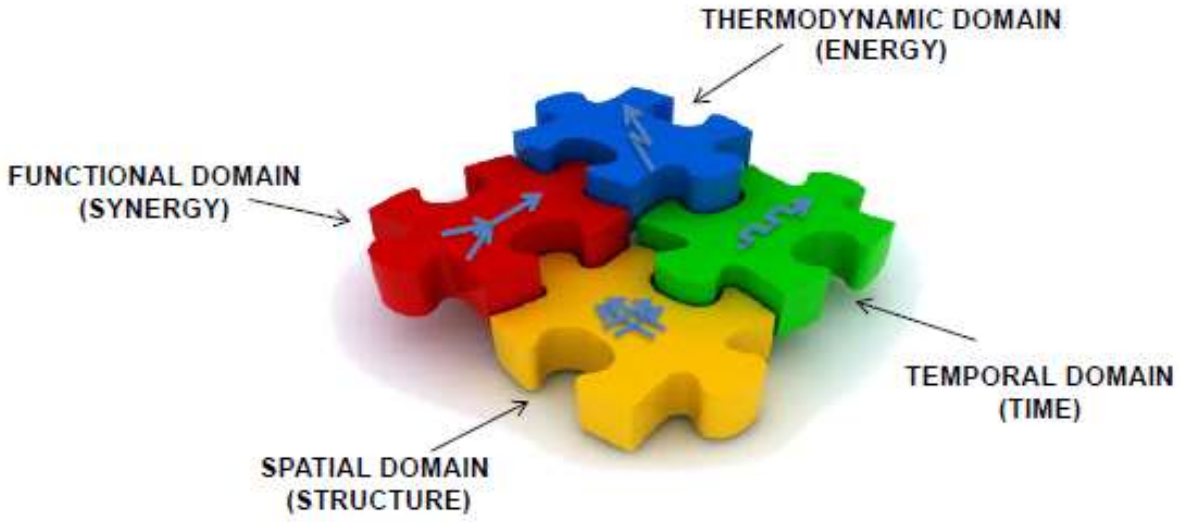
BTS / Miprowa plug flow reactor

Corning AFR™ G5 technology

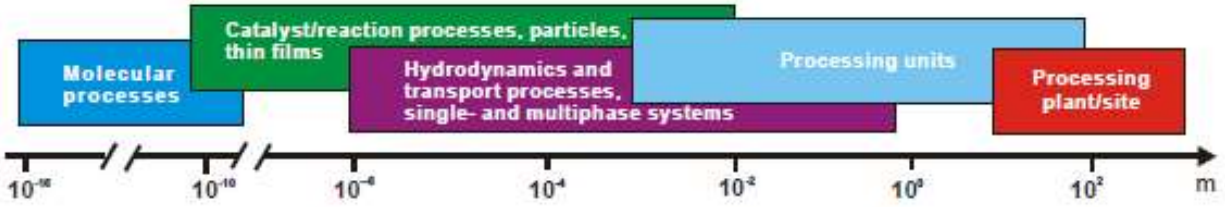
HEX-reactor

The benefits of continuous manufacturing

The breakthrough innovation via batch-to-continuous and process intensification



at all scales, from nano to macro



Van Gerven and Stankiewicz, IECR, **2009**, *48*, 2465-2474

C. Gourdon
INP ENSIACET

Acte III : qu'est-ce qu'on attend ?

C. Gourdon

Are there still any barriers in Flow Chemistry?

- Lack of technology / equipment providers?
- Lack of « proof-of-concept » (flexibility, polyvalence)?
- Development time too long / scalibility?
- Too few success stories?
- Cost (CAPEX)?
- Cultural?
- Missing link between chemists and chemical engineers?

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Unafic
Union Nationale des Associations Françaises d'Ingénieurs Chimistes

➢ Lack of technology / equipment providers?

No longer true in 2021 …

Miniaturization

fluitec
MEASURE. CONSULT. TREAT.

NJ BIO PHARMACEUTICALS

CORNING

vapourtec
precision flow chemistry

CHEMTRIX
Scalable Flow Chemistry

Zaiput Flow Technologies
Groundbreaking Innovations in Flow Chemistry

FLOWID

De Dietrich
PROCESS SYSTEMS

SYRRIS

EHRFELD
Mikrotechnik

NiTech
SOLUTIONS

Fraunhofer
IMM

C. Gourdon
INP ENSIACET

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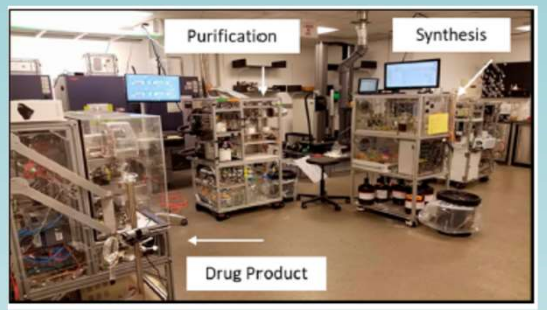
➢ Lack of « proof-of-concept » (flexibility, polyvalence)?
No longer true in 2021 …

➢ Public research Labs : since early 2000s

« Boostec » SiC pilot HEX-reactor born 2006 at LGC, Toulouse



Jensen Group, Org. Process Res. Dev. 2020, 24, 2183−2196

➢ Industrial research : modularization
-> multipurpose & flexible plants

Modular Pilot Plant, Maturity Level 4, at Evonik in Marl, Germany (Source: Phoenix Contact)

➢ Public Private Partnership : demonstration platforms (Toulouse, Graz, Glasgow …)

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➢ Development time too long?

No longer true in 2021 …

From lab process development to Industrial Production

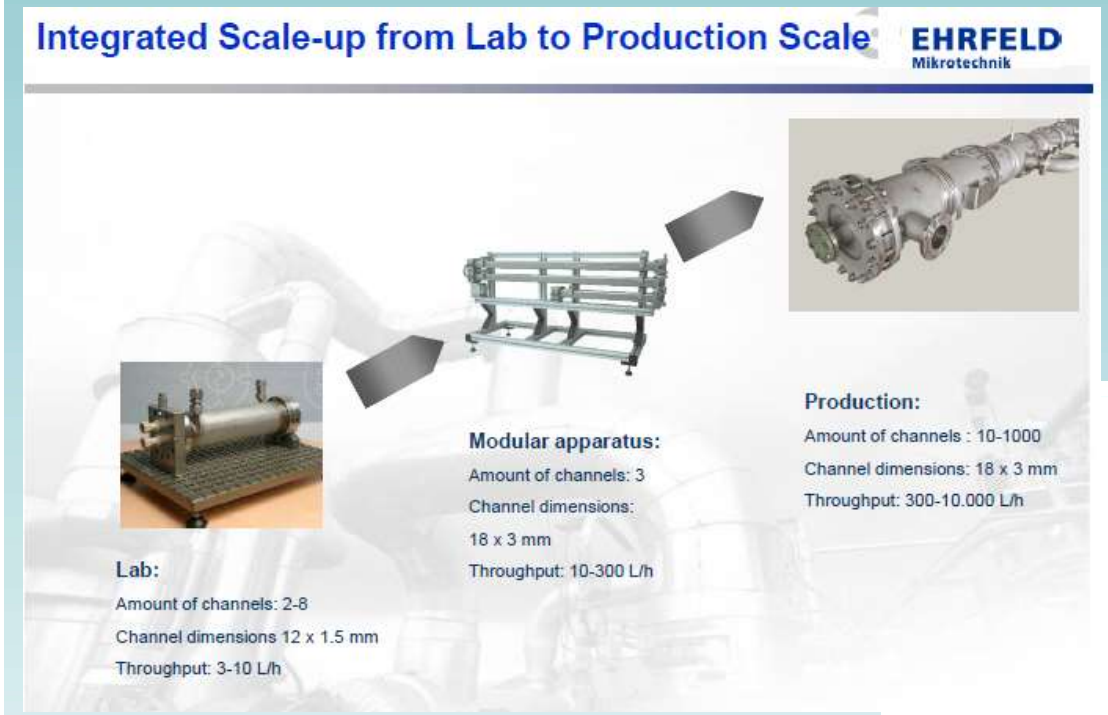
- In 9 months demonstration of a commercially viable approach to a cGMP nitration reaction

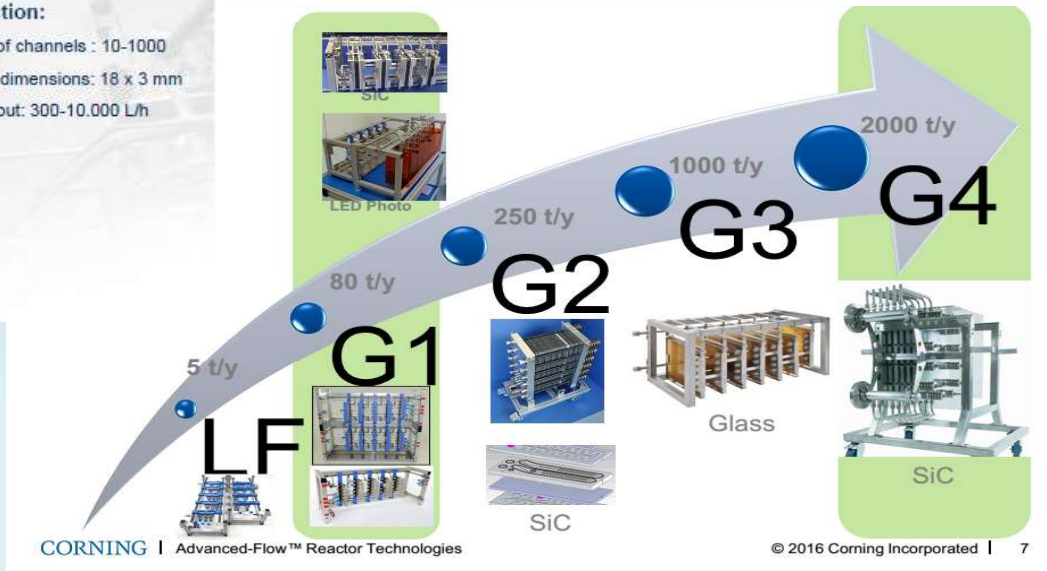
- Starting with 1 kg lab sample
- Parallelization of 8 identical reactors, integration into the production plant
- Execution of a campaign under cGMP conditions
- More than 25 mT materials processed
- More than 500 kg of quality product produced
- Safety performance and product quality were perfectly maintained

CORNING Corning Proprietary and Confidential | 6

➢ Scalibility?

No longer true in 2021 …





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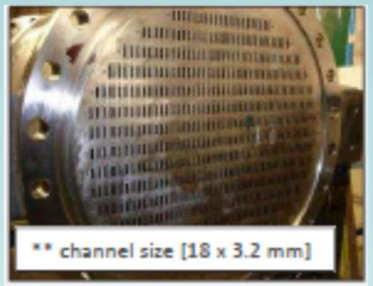
➢ Too few success stories?
Not really true in 2021 …

Miprowa® Reactors



Volume ca. 40 L
Throughput 5-10 kt/y

Courtesy Europic
www.europic-centre.eu

Advantages

- 100% capacity increase
- Significant yield enhancement
- Higher product quality
- Upgrade of safety
- Reduction of energy consumption & space footprint

Former process in about 20 batch reactors Volume 50 m³

Ehrfeld Mikrotechnik GmbH
Dr. Joachim Heck

PI-Technology name		**Varicol®**
Applied on industrial scale at		**UCB Pharma, Daicel Chemical Industries, Laurus Labs + several non-public references**
In the following process		**Chiral separation of racemic mixtures at multition scale (all) – public references include: Keppra® and Xyzal® (UCB), Lexapro®/Cipralex® (Lundbeck), Intermediate purification of omega-3 (Novasep)**
Country of application		**France, Belgium, Switzerland, USA, Japan, India, Denmark**
Year of application		**Since 2000**
Annual production capacity (place "X" where appropriate)	< 100 tons/year	**X**
	100 – kT/year	**X**
	1-50 kT/year	
	> 50kT /year	
Economic effects from the application (place "X" where appropriate)	< 100k$/year	
	0,100– 1 M$/year	
	1-5 M$/year	
	> 5 M$/year	**X**
Savings per category (fill in where appropriate)	Capital cost (%)	
	Labour cost (%)	**X**
	Raw materials (%)	**X**
	Energy (% or MW)	**X**
	CO_2 emission (%)	**X**
	Utilities (%)	**X**
	Waste generated (%)	**X**
	Product yield (%)	**X**
	Product purity (%)	
	Plant volume/equipment weight (%)	
Other (qualitative) effects		**(e.g. new product synthesis, fouling prevention, time-to-market, etc. – name the effect)**

Picture courtesy Novasep

Courtesy Europic
www.europic-centre.eu

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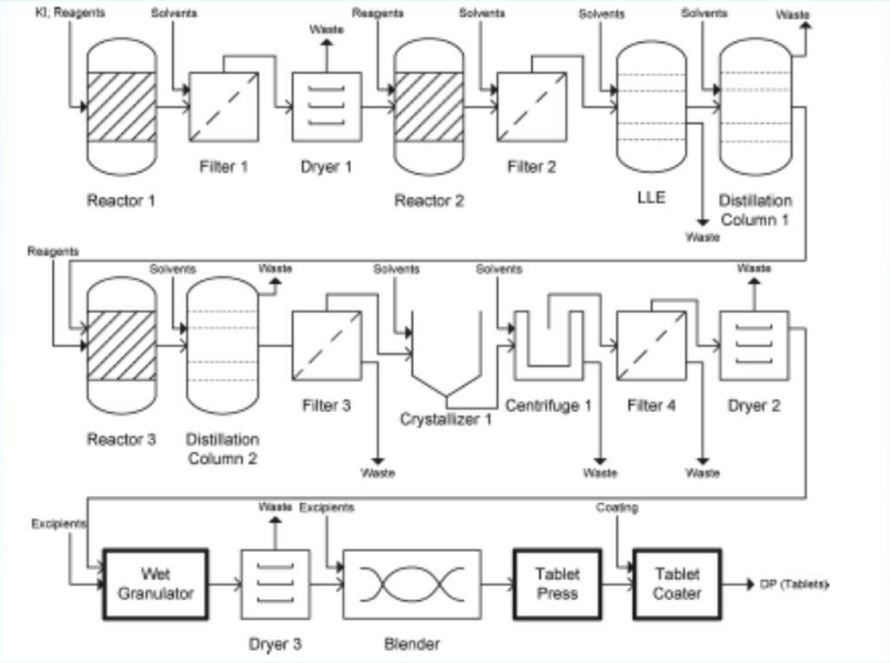
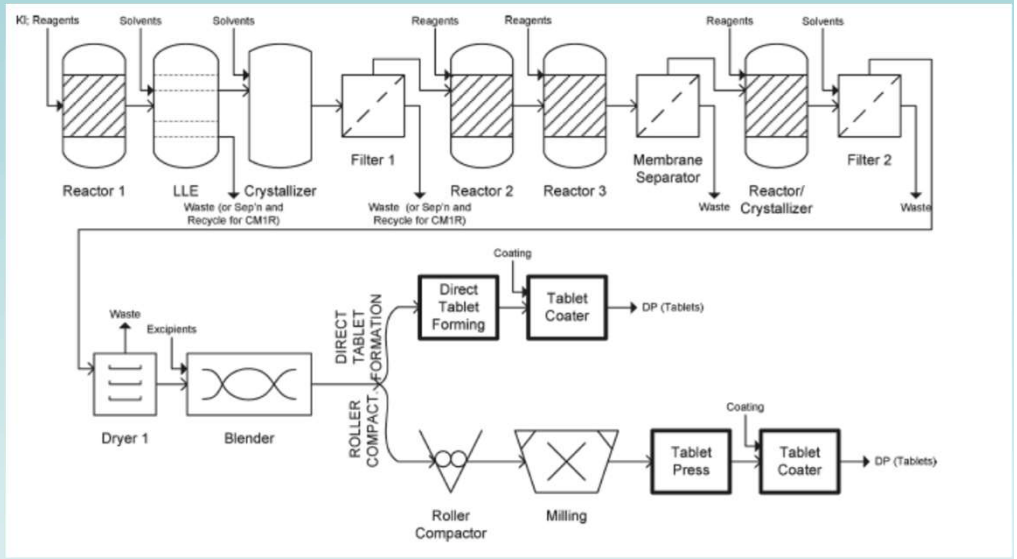
➢ Cost (CAPEX)?

Yes and No …

BATCH



CONTINUOUS



CAPEX: 20 to 76% lower

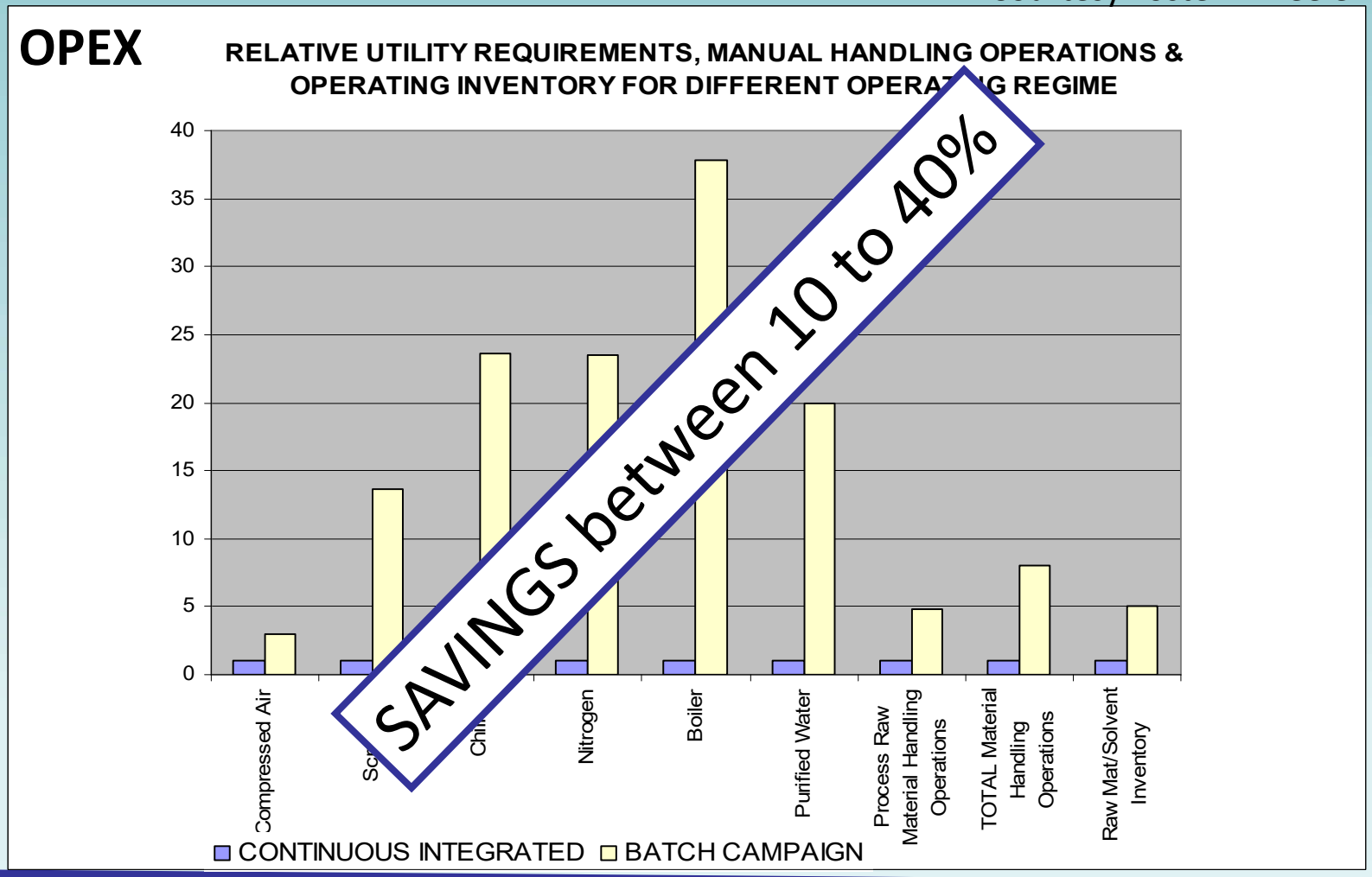
Schaber et al. dx.doi.org/10.1021/ie2006752 | Ind. Eng. Chem. Res. 2011

➢ Cost (CAPEX)?

Yes and No … see OPEX

Courtesy Foster-Wheeler

OPEX



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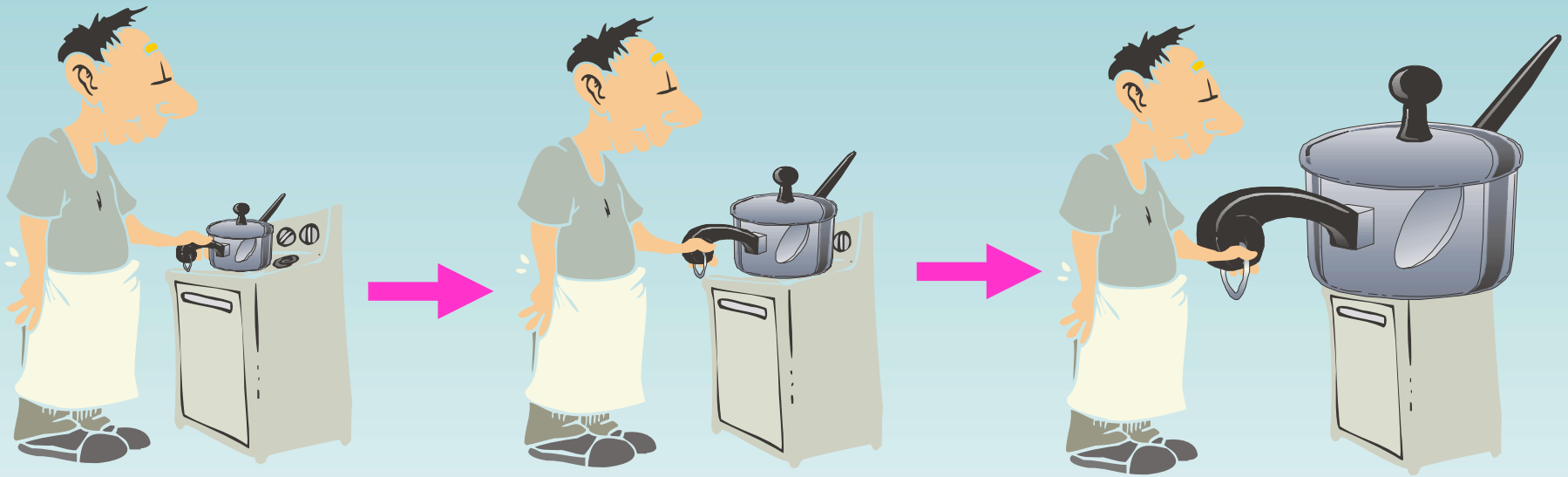
➢ Cultural?

Yes, a process born batchwise will end batch …



2 people

6 people

50 people

- Cultural?

  Yes, reluctance for innovation …

- Cultural?

  BUT, EDUCATION …

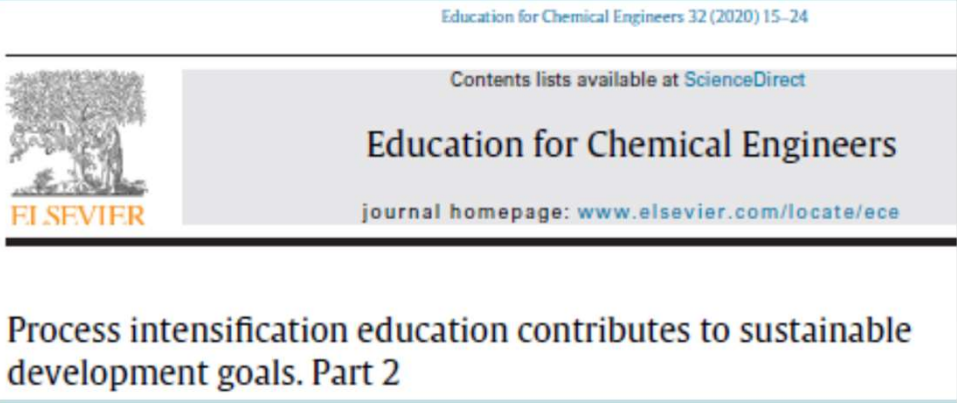

Education for Chemical Engineers 32 (2020) 1–14

Contents lists available at ScienceDirect

Education for Chemical Engineers

journal homepage: www.elsevier.com/locate/ece

Process intensification education contributes to sustainable development goals. Part 1


Education for Chemical Engineers 32 (2020) 15–24

Contents lists available at ScienceDirect

Education for Chemical Engineers

journal homepage: www.elsevier.com/locate/ece

Process intensification education contributes to sustainable development goals. Part 2

Parmi les 10 mesures-clés pour la chimie pharmaceutique préconisées par le Sicos (Vincent Touraille, Mai 2020) :

- Maintenir et développer la formation Chimie, Bac professionnels, IUT et Ecoles/Universités sur le long-terme

- Maintenir et développer les compétences et savoir-faire nécessaires sur le long-terme

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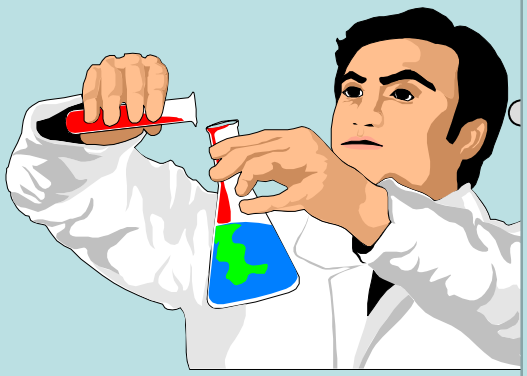
➢ Missing link between chemists and chemical engineers?

Chemical Process Development

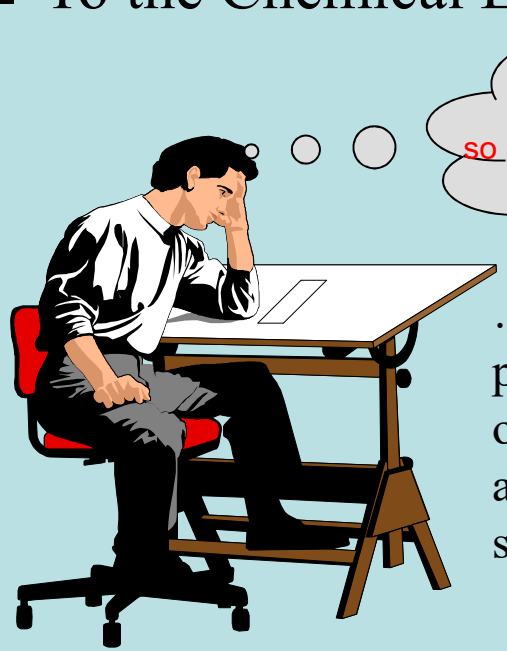
■ To the chemist…



…… Chemical Process de
the process conditions so
out in a glass flask - know
simply big versions.

Chemical Process Development

■ To the Chemical Engineer….



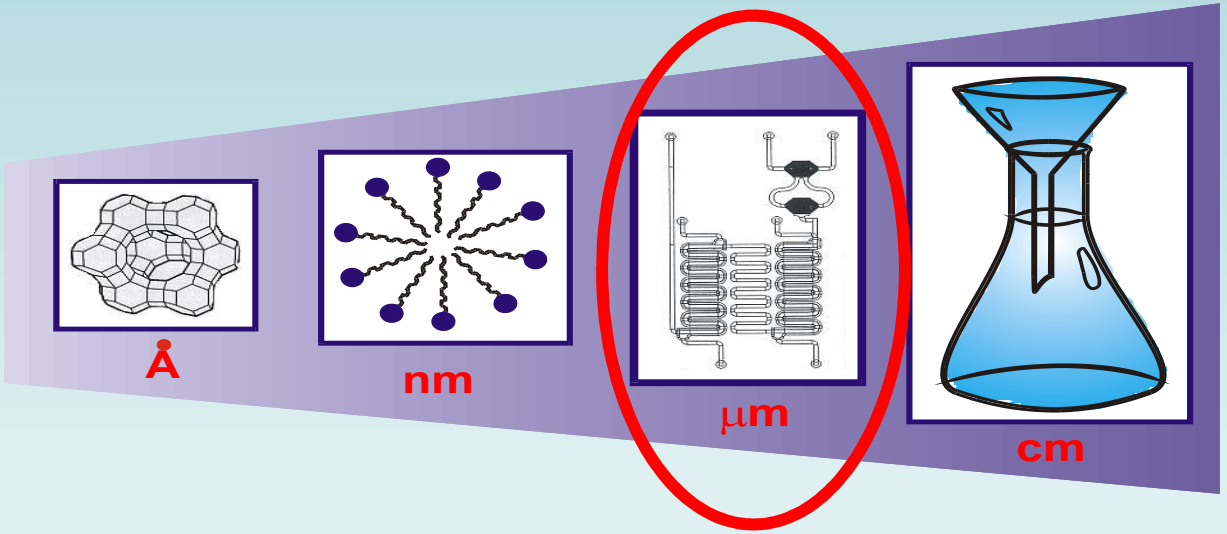
The jacket on the reactor will not give me enough heat transfer area so I will need to slow the addition down to control the heat flux

….Process development is about plugging together different unit operations to achieve an approximation to the conditions specified by the chemist.

➢ Missing link between chemists and chemical engineers?

No longer true in 2021 …

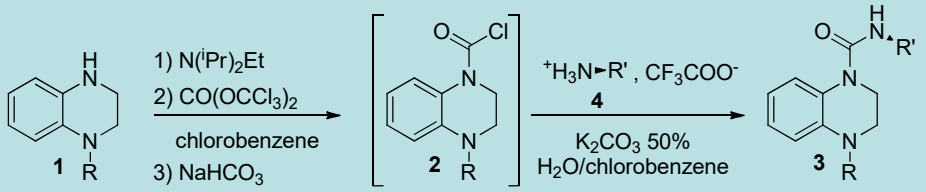
The missing link: microfluidics as reconciliation tool



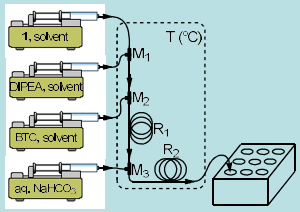
➢ Missing link between chemists and chemical engineers?

No longer true in 2021 …

Transposition of a triphosgene-based process for pharmaceutical development: from mg·h-1 to kg·h-1 of an unsymmetrical urea



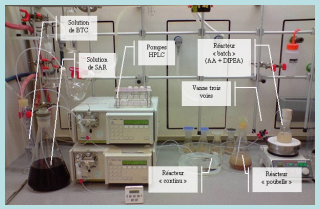
Experimental study
Parameters influence
(temp., ratio, residence time)



1 mg/h

Change in length
5 to 50 m

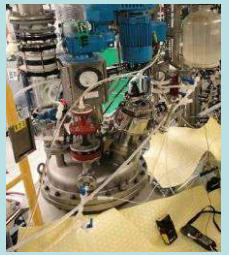
Hypothesis validation
at larger scale



1 g/h

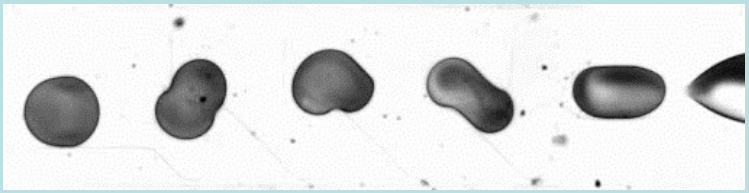
Change in size
.5 to 2.0 mm in ∅

Pilot plant implementation
in a milli-structured reactor



1 kg/h

SANOFI



F. Sarrazin, 2006 LOF/LGC

A 3-months project : FAST DESIGN METHODOLOGY

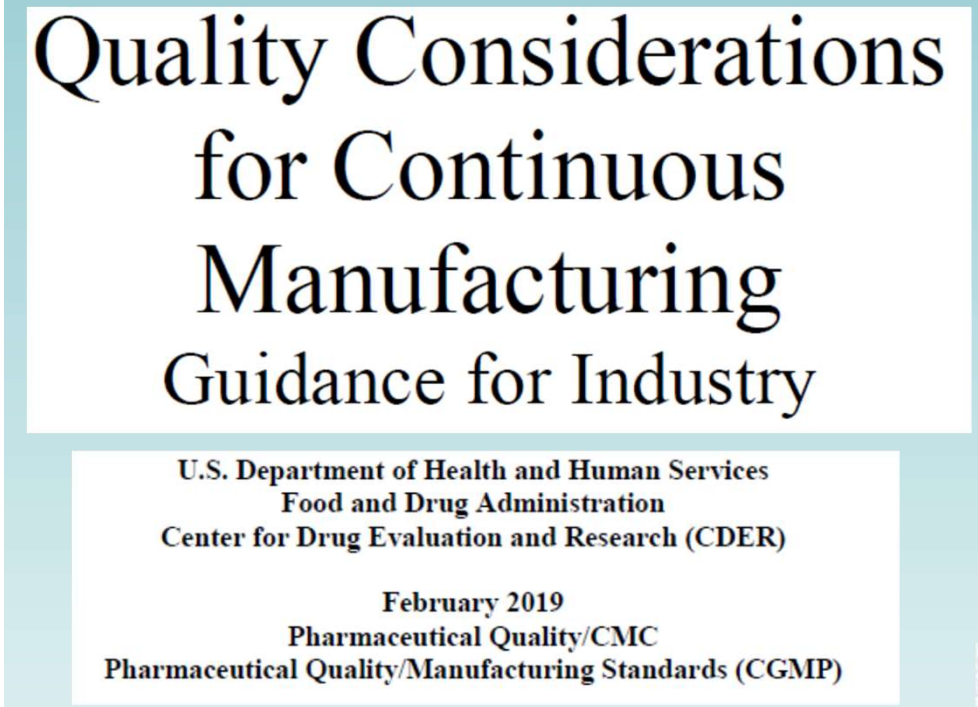
Leroyer et al., Green Processing and Synthesis, 2013.

Acte IV : perspectives et conclusion

Synthèse des principes actifs / Relocalisation par l'innovation
UNAFIC 30/03/2021

C. Gourdon

FDA context since 2019


Quality Considerations for Continuous Manufacturing

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

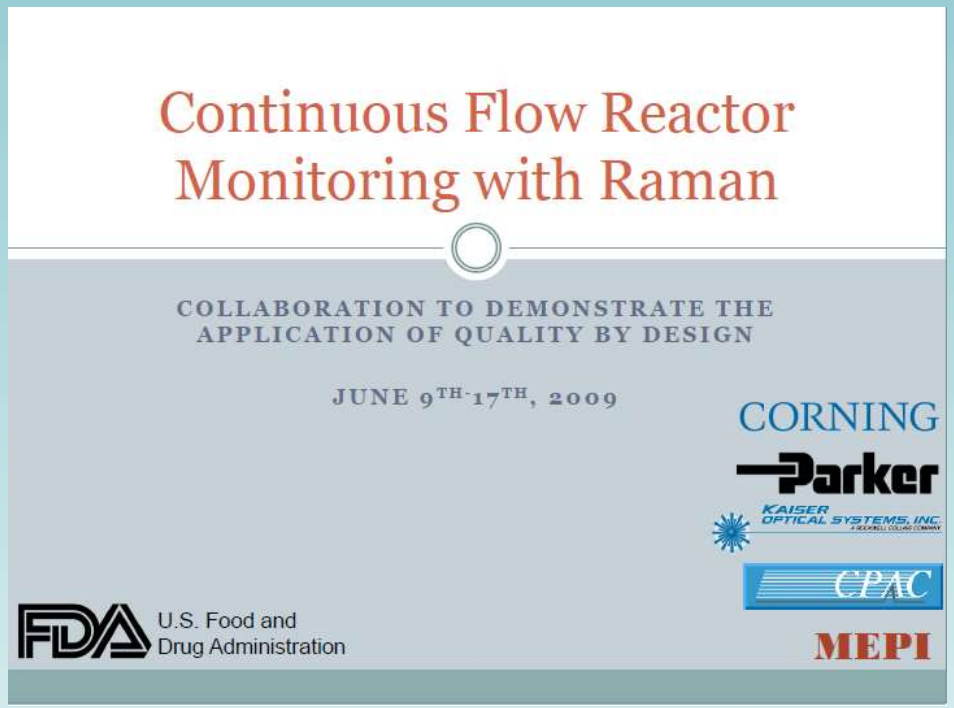
February 2019
Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Steady flow

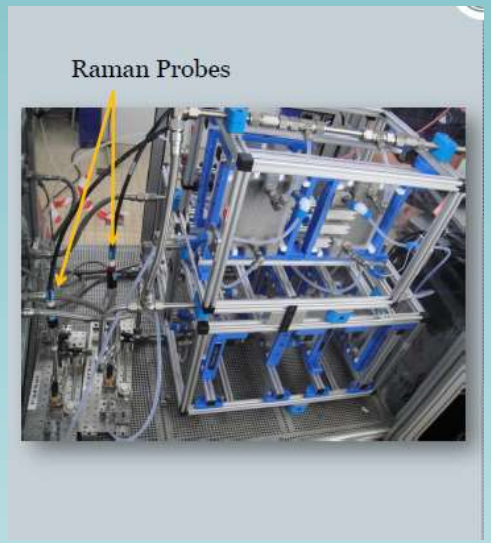
In 2020, the US FDA approved 53 new drugs …

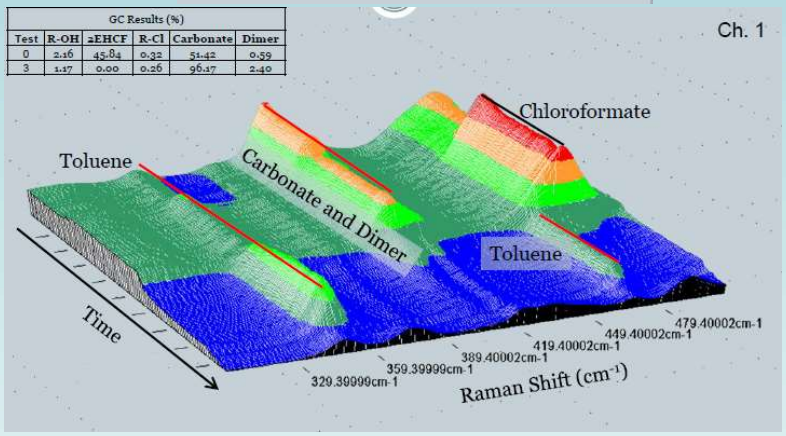
« Of those 53 new molecular entities, 35 were **small molecules** – which at **66%** of the total approvals continue to be a critical component of the drug pipe-line. »

JANUARY 11, 2021 | CEN.ACS.ORG | C&EN



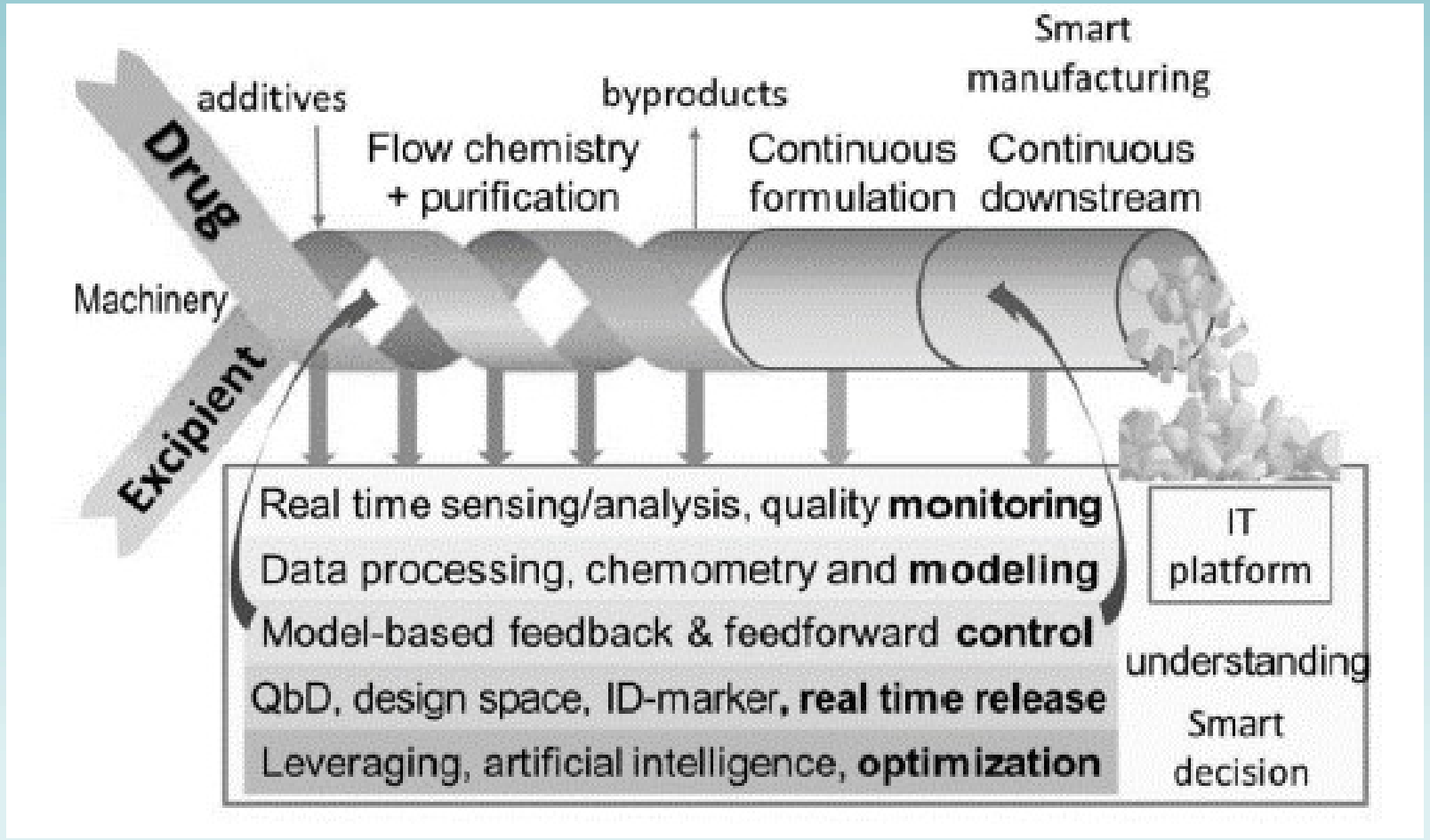
MEPI/CRITT Toulouse 2009





QbT -> PAT -> QbD -> QbC (real time control with feedback)

Concept of end-to-end continuous pharmaceutical Manufacturing: from raw materials to final products with real-time quality control



Org. Process Res. Dev. 2021
https://dx.doi.org/10.1021/acs.oprd.0c00504

Reaching Patient effectively & quickly – Continuous processing, a tool to change supply chain paradigm

DATE: **Wednesday April 28th, 2021**
TIME: **3:00 PM (CET) - 2:00 PM (GMT) - 9:00 AM (ET) - 6:00 AM (PT)**
DURATION: **MAX 2h**
OVERVIEW:

During this event you will learn how continuous processing can:
•Accelerate time to market e.g. Oncology
•Ensure high and constant quality
•Provide agility and flexibility to align on market demand

FREE REGISTRATION

Chairman and speaker:

Flavien Susanne
Head of Chemical Development and Engineering - Sanofi

Speakers:

Andrew Rutter
Director at rutterdesign
Nick Thomson
Senior Director Chemical Research and Development at Pfizer
Rob van Dongen
Senior Basic Design engineer and lead development, Pharma Group - Zeton

(Re)-localisation industrielle ?

➢ **OUI** grâce à l'innovation

et à la formation (nécessaires … **MAIS** insuffisantes)

➢ **CAR, PAS SANS** évolution des politiques et modèles économiques

- Pouvoirs publics (invest. UE, souveraineté 'made in Fr', aides-AMI, territoires …)
- Secteur industriel (supply chain, proximité client, ETI …)

➢ Des voies alternatives « Privé-Public » (exemple CIVICA aux USA) ?

(cf rapport Biot 2020
« Mission stratégique visant à réduire les pénuries de médicaments essentiels »)

« La meilleure relocalisation est une délocalisation qui n'a pas lieu »

Les cahiers du cercle des économistes, 4/02/2021

Merci pour votre attention

christophe.gourdon@ensiacet.fr