ECA
European Compliance Academy

The University of Heidelberg
QbD / PAT Conference 2014

Continuous Manufacturing for Small Molecule APIs

Peter Poechlauer, Oct. 2014

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Contents

- **Who is DPx ?**
- **Process Understanding and Process Control**
  - „understanding" a process
  - science-based process models
  - "control" the process both to keep it within the design space and to allow for continuous improvement.
- **Regulatory Aspects**:
  - definition of batch / lot
  - from a control strategy based on analysis of batches to a control strategy for manufacturing processes consisting of a mix of batch and continuous steps.
- **Business Aspects**:
  - fields of activities where the changeover to continuous manufacturing has proven to be profitable
  - drivers to select a continuous manufacturing option
  - key success factors in implementing a continuous process.

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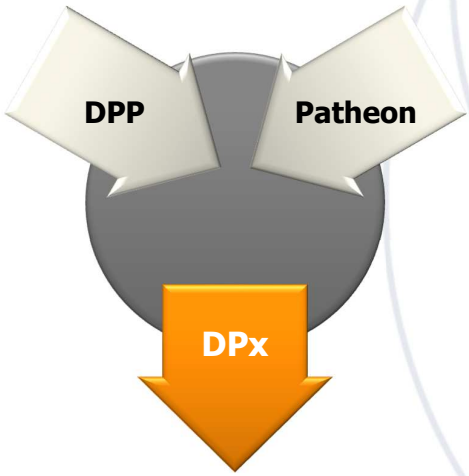
Patheon and DPP are merging to provide comprehensive Manufacturing & Development Services to the Pharma Industry

- **DSM Pharma Products (DPP)** and **Patheon** are now the leading comprehensive contracted service provider in the pharmaceutical industry

- **Patheon**
  - Pharmaceutical services
- **DSM Fine Chemicals**
  - APIs, fine chemicals and intermediates
- **Banner Life Sciences**
  - Pharmaceutical and nutritional products



Patheon Performance the World Over®

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BANNER LIFE SCIENCES

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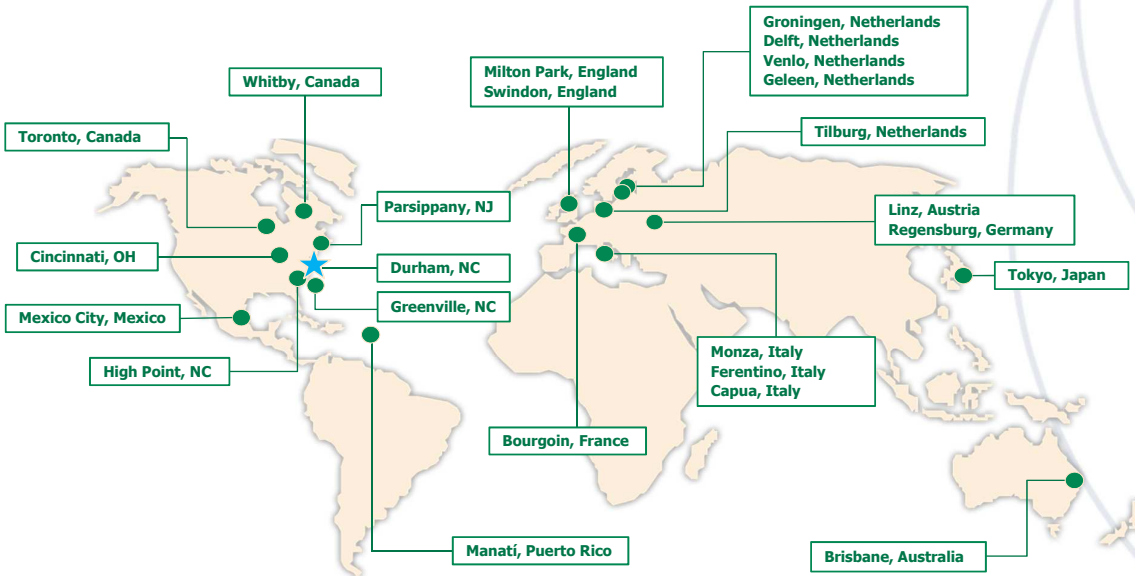
An Integrated Network of 24 Locations around the World for API, Drug Substance, Development and Manufacturing



13 commercial-scale finished dose form facilities, 4 API manufacturing and development operations, 4 biologic drug operations and 9 pharmaceutical development centers

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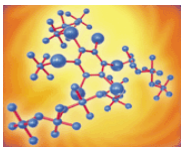
DPx Fine Chemicals Austria - History



„Stickstoff Chemie"

Base Chemicals

Fine Chemicals

Pharma Chemicals

DPx

1939 1970 1980 1996 2010 2014

Fine chemicals production…

Fine chemicals suppliers

…must improve their process knowledge and their concepts to ensure product quality

…can no longer rely on any lasting "advantage of superior technology" to stay competitive.

…have to meet rising environmental standards on transport and inventory, emission and efficient use of energy and chemicals.

…have to develop processing concepts that are intrinsically competitive (not by law or by protection)

…are socially accepted

…will undergo changes comparable to other industries

Compliance, quality

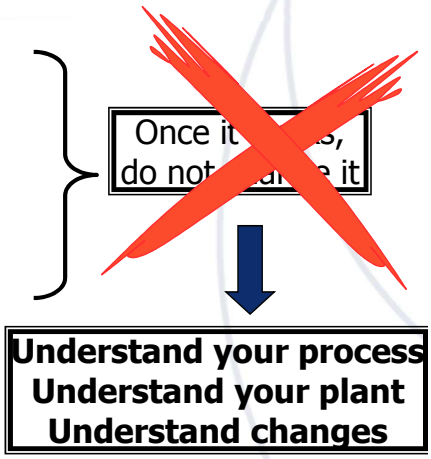
Sustainability, greenness

Fine chemicals manufacture: priorities

Compliance, Quality:

Reliably and reproducibly meet
high quality standards of process and product

- With less quality risk during scale-up or plant change
- At reduced cost of control and supervision
- With less rejected or off-spec material produced



Sustainability & Greenness:

Design new or improve processes & plants
that allow to produce

- Safer cheaper & quicker (shorter start-up time)
- More eco-efficient (footprint, process mass intensity)
- Existing materials from renewable sources
- Using new chemistries not scaled up so far

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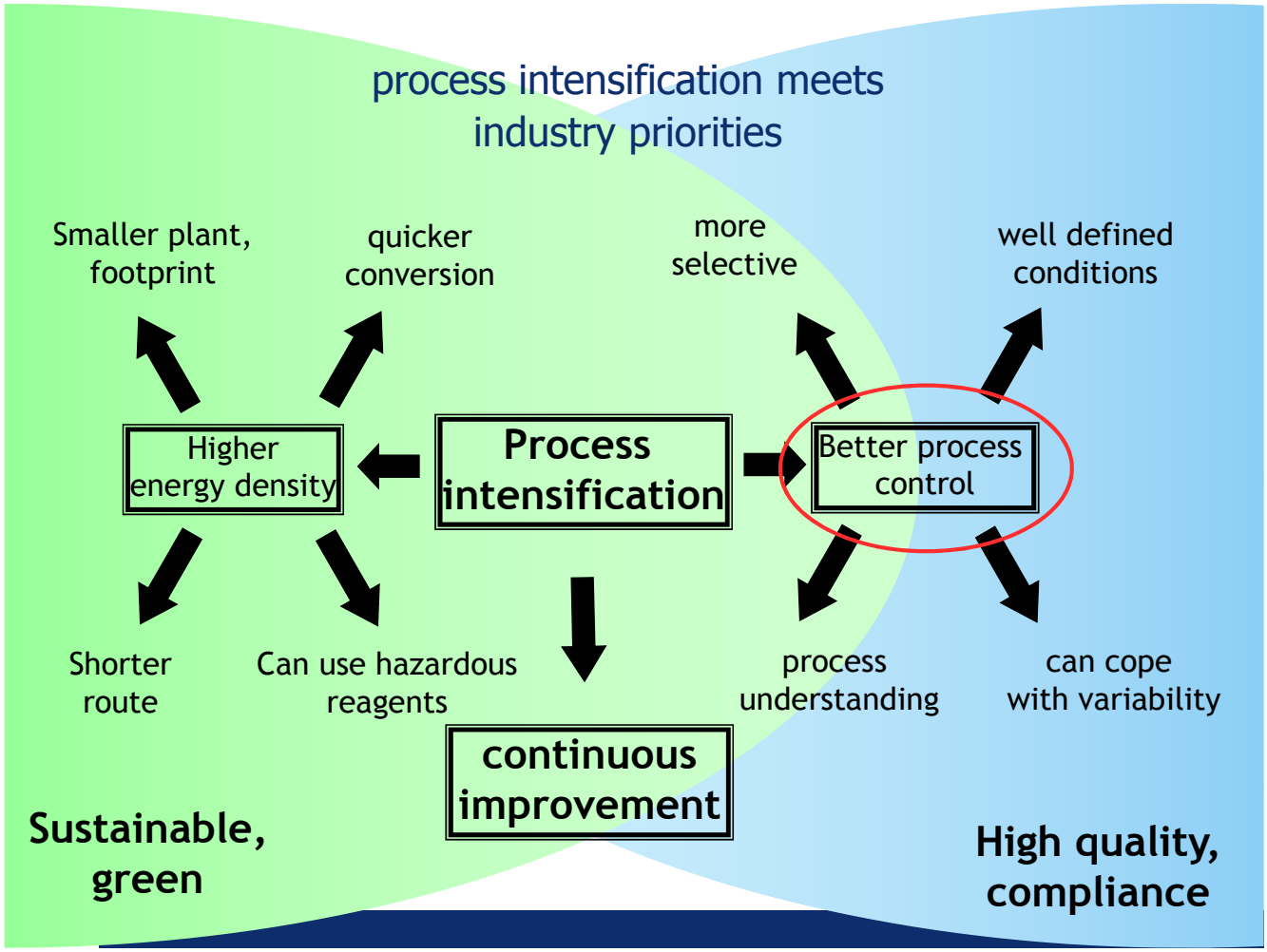
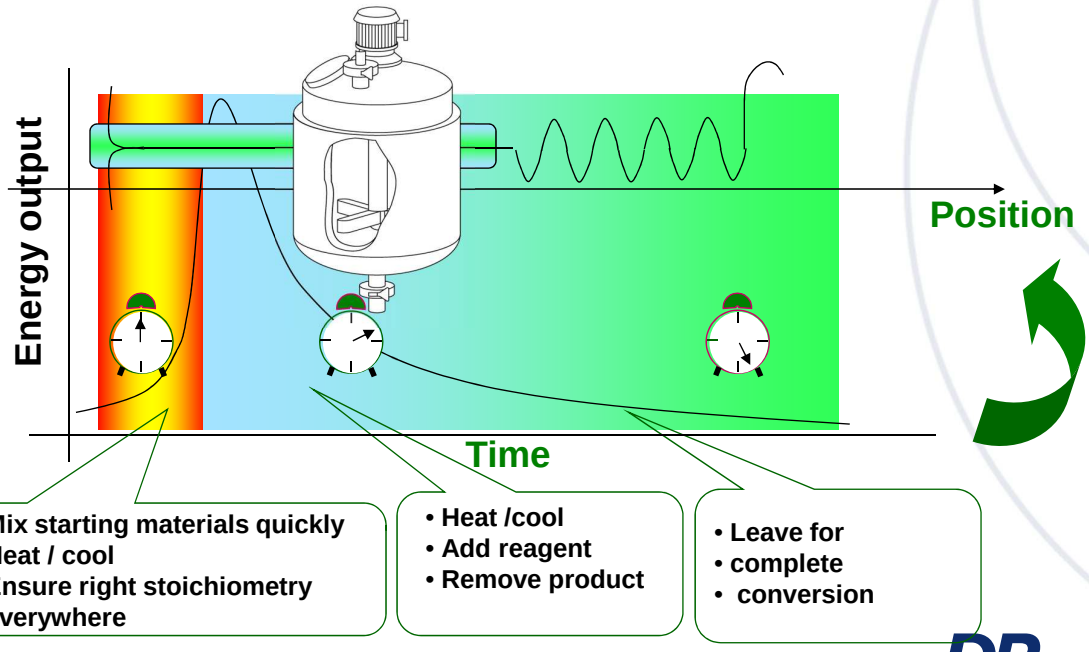


Quality and control: the ideal reactor …

Quickly provides ideal conditions for every phase of the reaction:



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Compare: process control…

Batch recipe:

Start stirrer

Heat jacket to.. C

Add …kg of A

Add in total …kg of B

at a rate to keep

the temperaure below… C

Stir at .. C for ..more hours until IPC ok.

Continuous flow recipe:

Heat system to.. C

Add A at a rate of…kg/h

Add B at a rate of…kg/h

(..until batch has desired size.)

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..and its effect on „quality by design"

A definition of „Quality by design" states:

- Variability is controlled by the process
- All critical sources of variability are identified and explained
- Product quality attributes can be accurately and reliably predicted over the design space established for
  - materials used,
  - process parametres,
  - environmental and other conditions

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Compliance: Guidance for pharmaceuticals manufacturing: "understand your process"

- **ICH Q8: "Pharmaceutical development":**
  - to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- **ICH Q9: "quality risk management":**
  - to offer a […] systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.
- **ICH 10: "Pharmaceutical quality systems":**
  - To establish, implement, and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities etc.

The basis of compliance with these guidelines is a sound scientific understanding of the manufacturing process

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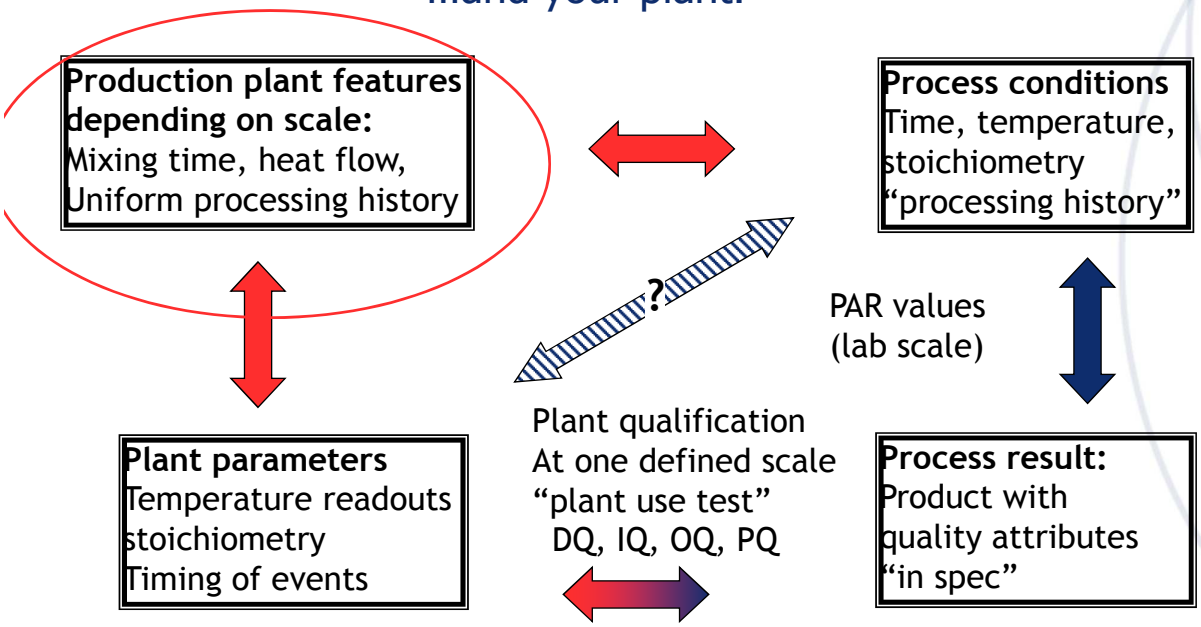
ICH = The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

understand your process…
…and your plant.



…Plant understanding

…Process understanding

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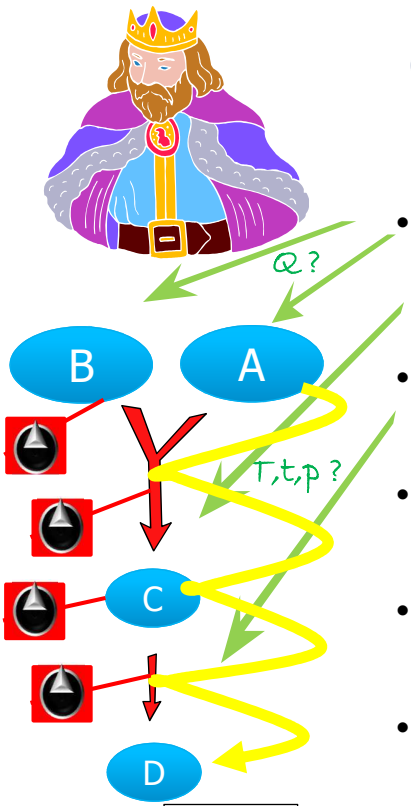

GMP, Quality and trust

- Identify **critical material and process parameters** affecting product quality (using prior knowledge, risk management tools, DOE, MVA).
- Understand and if possible express mathematically their relationship with the **critical quality attributes**.
- Design a **process measurement system** to allow on-line or at-line monitoring of critical quality attributes.
- Design a **control system** that will allow adjustment of critical quality attributes.
- Implement a **quality system** that allows **continuous improvement.**

From: **Quality Assessors Training, Oct 2009**
Evdokia Korakianiti, PhD, Quality Sector, EMEA

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Continuous processes emphasise the PAT principle: "Quality cannot be tested into products; it should be built-in or should be by design"

- Easy set up and verification of design space due to few process variables
- Easy process control (steady state) due to few process variables
- Reduction of cycle times
- Real time product release
- Prevention of reject product
- Increased use of automation
- Facilitation of continuous processing using small-scale equipment, resulting in improved energy and material use and increased capacity.

Source: SSCI I

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Equal qualification approach on batch and continuous processes (Q7A)

Qualified asset

- Qualified analytical equipment
- Validated analytical methods
- Validated process

Qualification:

- flow reactor has no moving parts, operates at steady state. Qualification is easy
- "many" thermometers, manometers,
- "many" flow meters, measuring at unusually low flows.
- interesting: detailed investigation of potential backflow scenarios
- common supply with water etc.: -separation advisable.

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Definition of lot, batch

21CFR 210.3 defines "batch" as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture".

As the FDA points out, this does not specify the mode of manufacture.

21CFR 210.3 defines "lot" as "a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits;

or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits".

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analytics status at Current API process

- process understanding via thorough research on steady state.
- identification of critical control variables using multivariate techniques
- development and validation of appropriate analytical methods for measuring critical control variables
- qualification of on-line analytical technique (boundaries by limited availability of 21 CFR software)
- transfer of analytical methods to on-, in-, or at-line use on qualified equipment.

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The business case of continuous manufacturing

A business case

…analyses a particular scenario concerning the ***profitability*** of an ***investment opportunity***.

…presents and compares the projected financial and strategic impacts of ***different options for action***.

"***Action***", from a business perspective, will always be understood as "***investment***".

(WIKIPEDIA)

9 member companies of the "ACS Green Chemistry Institute® Pharmaceutical Roundtable" teamed up

to show that the introduction of continuous manufacturing is an attractive business option – and makes processes greener.

See: Org. Proc. Res. Dev. **2013**, *17* (12), pp 1472–1478

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Business Case for Continuous Manufacturing: Approach

A

1. **scoping**; shaping of "single cases":
   Where do we see them? Define fields of activities
2. **describing** single cases:
   What has been done? motivation / effort / value
3. **reporting**, collecting cases

↓ Analysis:
Why was a continuous process chosen as best option for a certain synthesis?

B **Drivers** to implement continuous manufacturing

↓ Analysis:
What are key success factors of successful implementations?

C **Crucial elements** of implementation

↓ Analysis:
Do the single cases reflect the principles of Green Chemistry? How?

D **Relation** of continuous manufacturing and Green Chemistry

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A Cases in different company activities :

	lead generation / optimization / pre-clinical	early / late clinical development	route optimization	production process for launch	primary / secondary manufacturing	second generation processes
materials / waste savings		BM; JC	BM; PP; JC; EF	BM; PP; JC; EF	JC	BM; JC
smaller footprint / smaller plants	AO	AO	PP; JC	PP; JC	PP; JC	PP; JC
company goals (CO2 emission)			PP; JC	PP; JC	JC	PP; JC
investment for new processes / plants		ML;				
green reputation			EF; ML	EF; ML		
local production						JC

17 single cases analyzed

several answers | single answer | envisaged, but no answer

B Drivers to implement Continuous manufacturing…

…are specific features of

- chemical reactions
- unit operations
- chemicals themselves

that render continuous processing especially attractive.

We identified 12 drivers in 3 groups:

- Logistics / quality
  - Throughput; right first time; minimization of inventory
- Chemistry / process drivers
  - Very high or very low temp.; unstable IM; demanding separation
- Safety
  - Very exothermic; high pressure; no vapor space; highly potent or cytotoxic material

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Key success factors: Crucial elements for implementation

Many groups experienced similar pitfalls related to equipment failure or misjudgement of the effects of deviations.

They developed routines and "best practices" to accomplish certain tasks. Certain topics appear systematically in the reported cases of successful implementations.

Moving (pumping) process flows:

- tolerable deviations from constant flow? (related to stoichiometry)
- properties of medium: Boiling point, viscosity
- Homogeneous? Gas-liquid? Slurry?
- pressure? pump or press?

Keeping process medium at defined conditions for defined time

Relates to „selection and design of continuous reactors"
„plug flow with dispersion"?
„continuous stirred tank"? cascade?
depends on reaction rate (🡐 reaction temperature)

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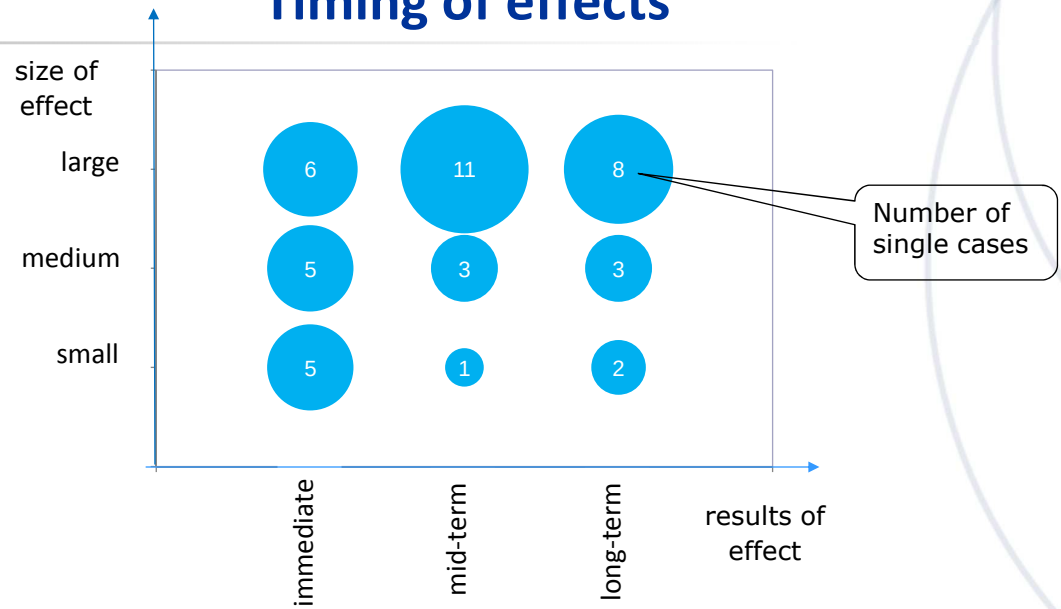
Crucial for implementation: Timing of effects



Most cases (not random sample) show large effects, either with immediate or mid-term results.

This reflects the trend to develop this technology within or in close collaboration with business projects, **not as a separate effort**.

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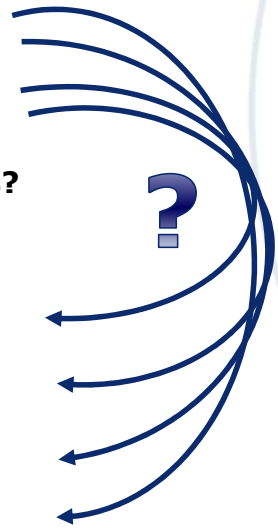
D Continuous Manufacturing
Value Categories vs. greenness

Many of the cases contain as specific advantages (value categories):

1. Increased development speed
2. Higher process reliability / product quality
3. lower investments in hardware
4. Safely scalable hazardous chemistry



How do we translate these into green arguments?

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feed-stocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

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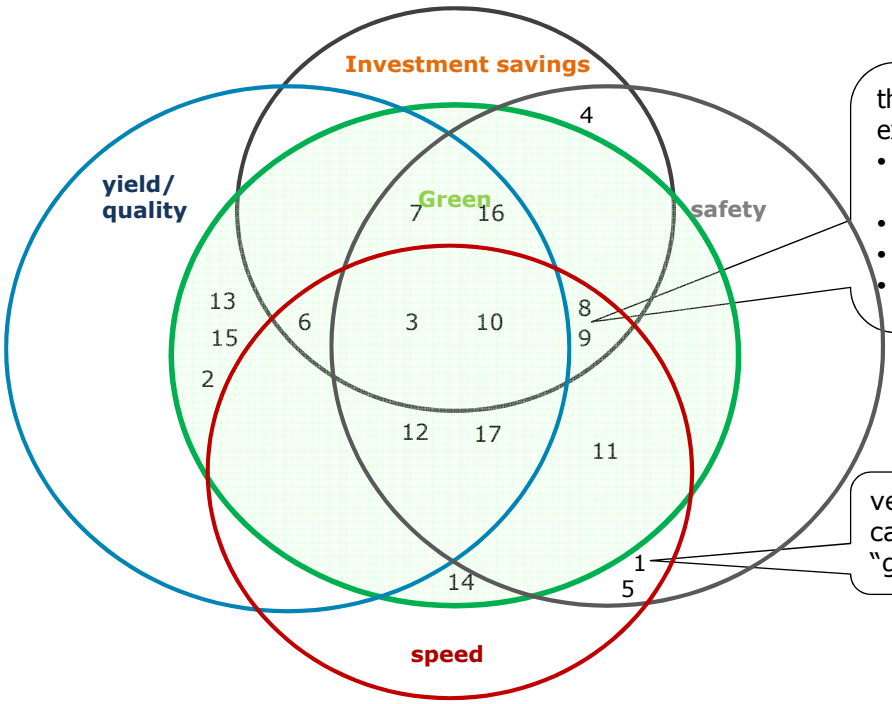
D Continuous Manufacturing
Value Categories vs. greenness



this position denotes: example describes
- catalytic process (green)
- gains in safety,
- lower invest,
- higher speed

very few "business cases" are outside "green circle"

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Examples: low-temperature **metalations in flow**

Temperature range:
Metalations in flow can operate at higher temperature (20-40 C higher).
The temperature difference between reaction medium and coolant is smaller.
➔ **cheaper cooling power,** easier in scale-up.

Time demand:
As many metallo-organic agents are highly reactive,
the cooling rate determines the time demand of their use in batch
already on 2-5 liter scale .
Flow metallations operate as fast as the chemistry allows

Productivity:
Already on laboratory scale differences in byproduct formation occur,
by deviating process conditions:
-wrong stoichiometry (slow mixing of reagents).
-wrong temperatures (hot spot formation).
Both effects become worse in a large batch vessel.

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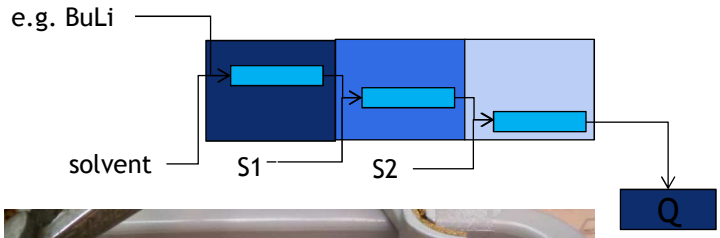
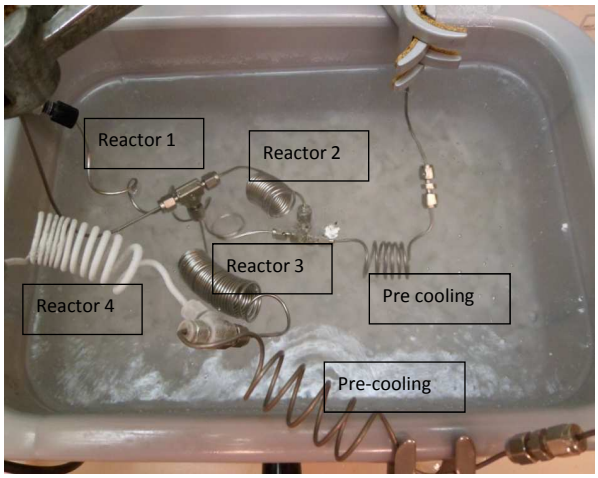
low-temperature metalations in flow – how?

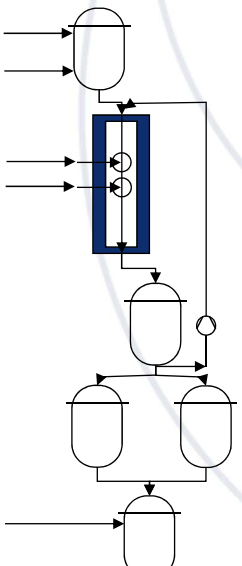
in the laboratory: quick and simple:





determine
- temperature
- temperature effects
- residence times 1,2,3
- stoichiometry
- issues (clogging?)

in the plant: integrate into existing devices:



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low-temperature reactor in pilot plant… & PLANT

… flexible, quick, robust

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There is 1
critical issue:

Deal with
non-believers
(Steve Ley, Cambridge)

Jacob Jordaens (1593 –1678), from wikicommons

Conclusions

- Continuous processing in the manufacture of pharmaceuticals is moving from embryonic to maturity.
- It simplifies QbD solutions that meet authorities' guidelines
- Flow Reactor Technology is ready for implementation and will:
  - Shorten development times
  - Improve productivity and safety
  - Open up new domains for pharma chemistry

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