Sustainable Manufacture of Fine Chemicals by Flow Processes

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HEALTH · NUTRITION · MATERIALS

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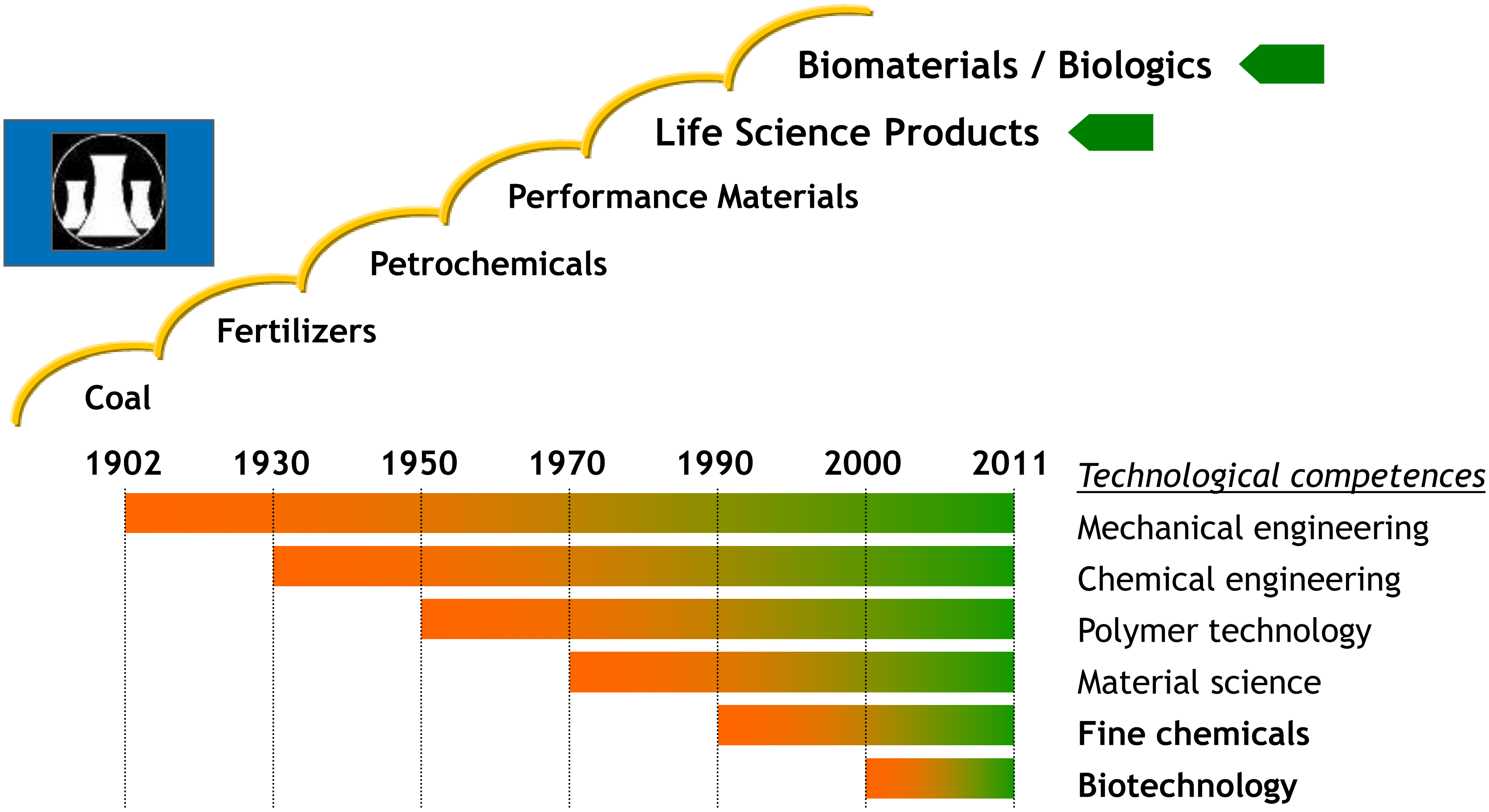
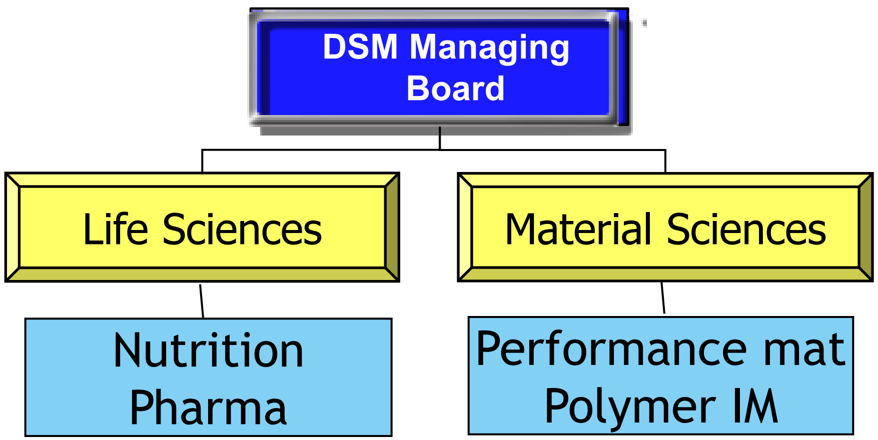
Content:

- Who is DSM?
- The fine chemicals industry – present boundary conditions – present priorities
- flow processes meet industry priorities
- Process intensification: how?

DSM Corporate Sustainability– A Century of Successful Self-Transformation

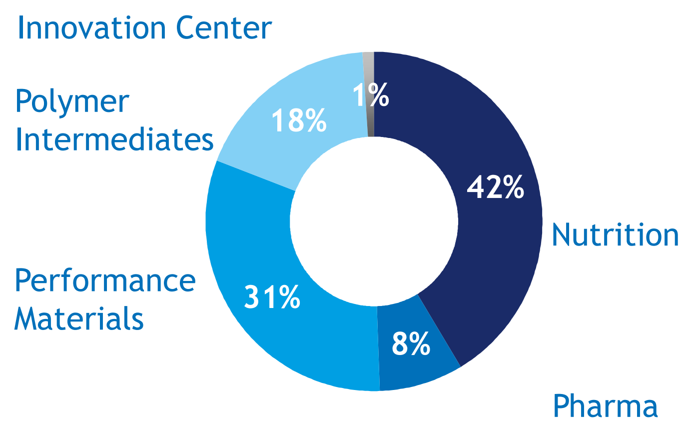


DSM: A Global Leading Life Sciences/ Material Sciences Company



- Active in 49 countries,
- 5 continents, 200 locations

Sales(*) per cluster



(€ million)	2012
Net Sales	9,131
EBITDA	1,109
Net profit	437
ROCE	8.9%
R&D	490
workforce	23,498

Dow Jones Sustainability World Index
DSM has been #1
in the Global Chemical Industry 5 of 7 years

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what keeps us in business ?

O. Zechyr, “1000 Jahre Linz”

A. Stankiewicz, Transforming Chemical Engineering

our customers think that there are
4 major drivers for future development:

- quality / trust
- sustainability / greenness
- variability of chemistry
- flexibility of production

Continuous flow technology has an answer to each

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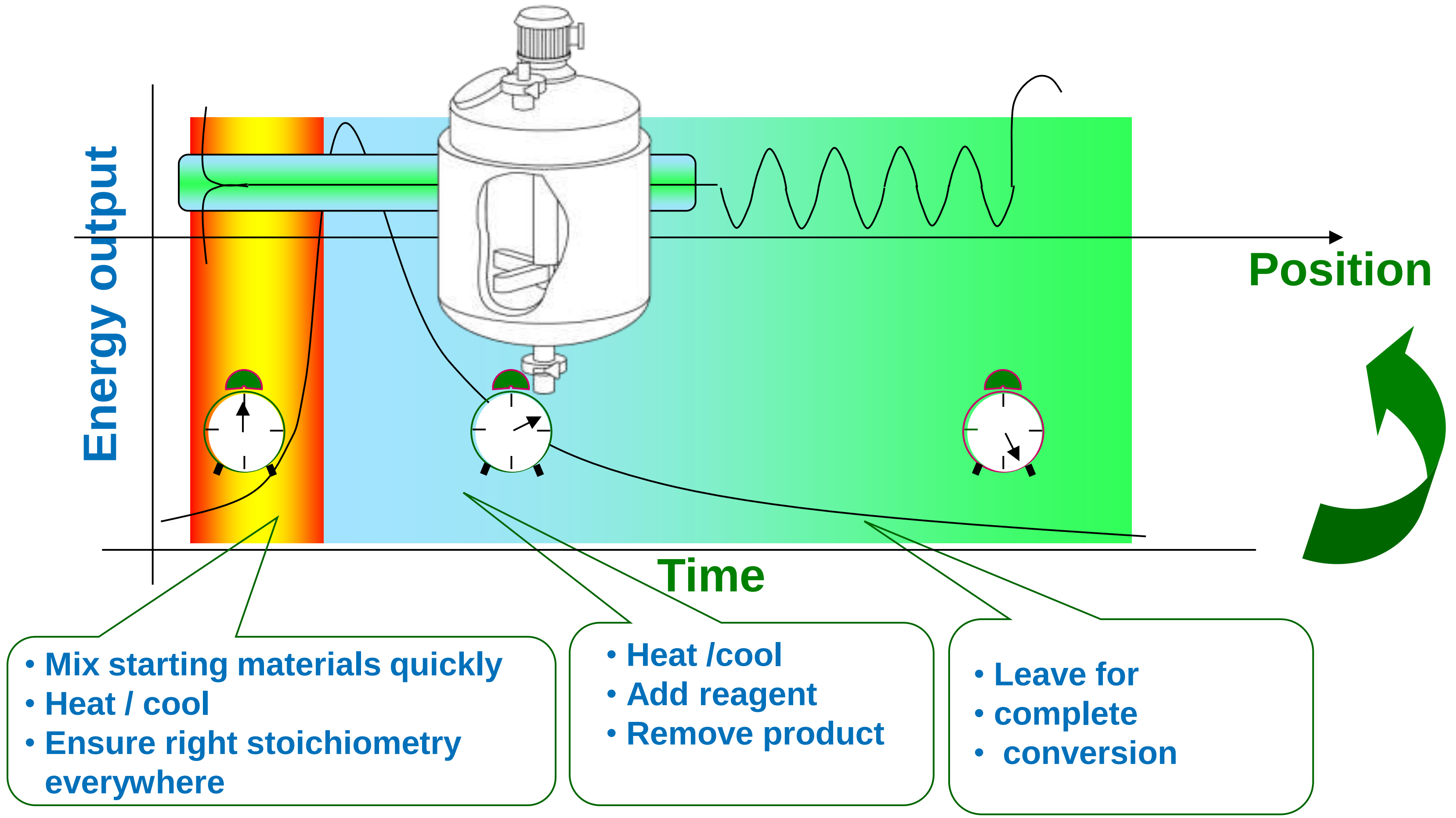
Quality & trust: the ideal reactor …

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.)

..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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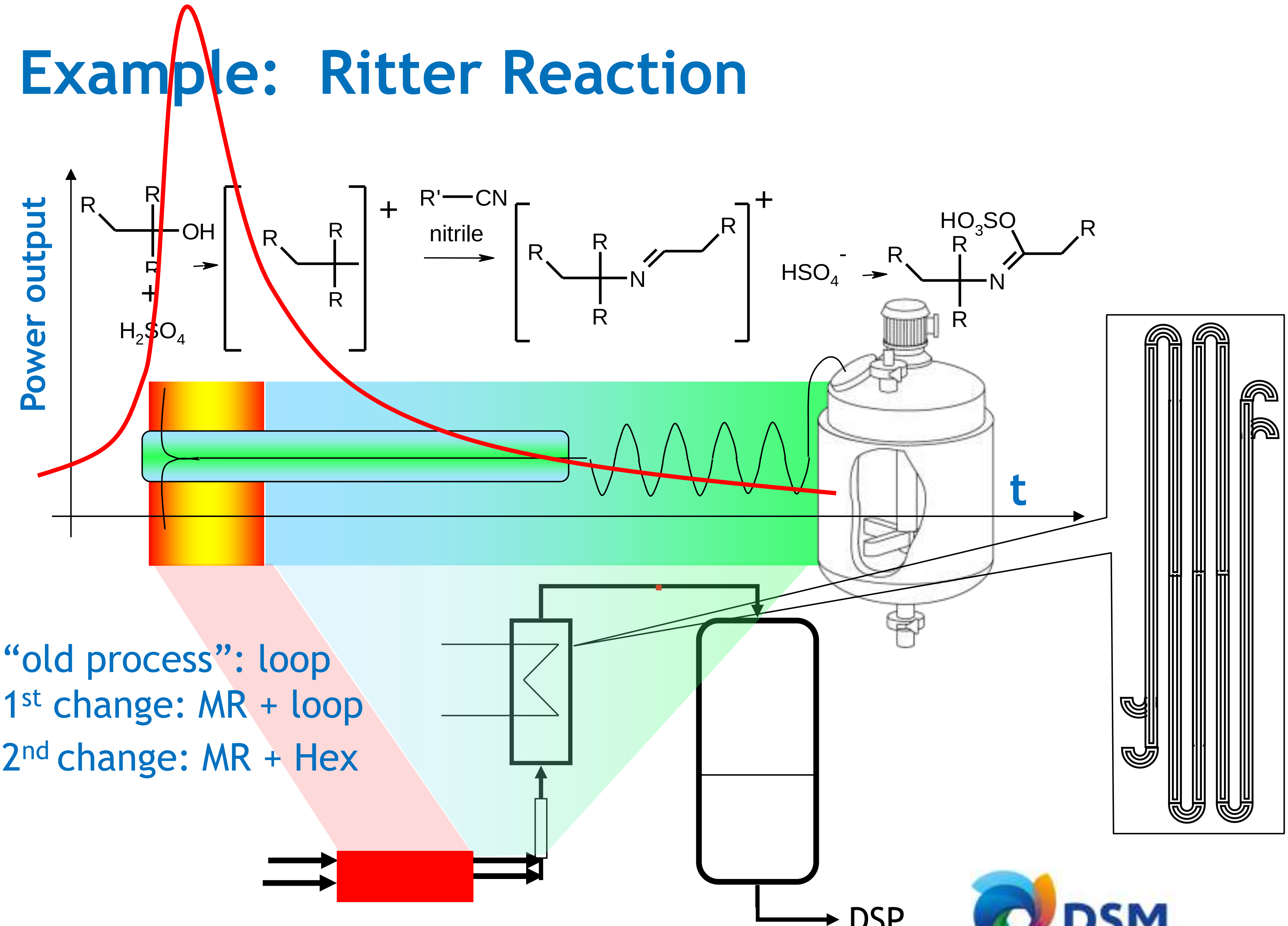
Example: Ritter Reaction



“old process”: loop

1st change: MR + loop

2nd change: MR + Hex

sustainability / greenness

the following technologies will further grow in importance:

- chemocatalytic and biocatalytic methods will win over stoichiometric methods

- supply and use of high-quality starting materials and intermediates from sustainable sources
  (green economy vs. fossil economy)

- methods using solvents and reagents that are "sustainable according to agreed metrics": the "GCI® pharma round table" has edited "key green engineering areas[1]" to define the focus:
  - Continuous Processing,
  - Bioprocesses,
  - Separation and Reaction Technologies,
  - Solvent (Selection, Recycle and Optimization),
  - Process Intensification

1. C. Jiménez-González et.al., *Org. Process Res. Dev.*, **2011**, *15* (4), pp 900–911.

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Sustainability of production

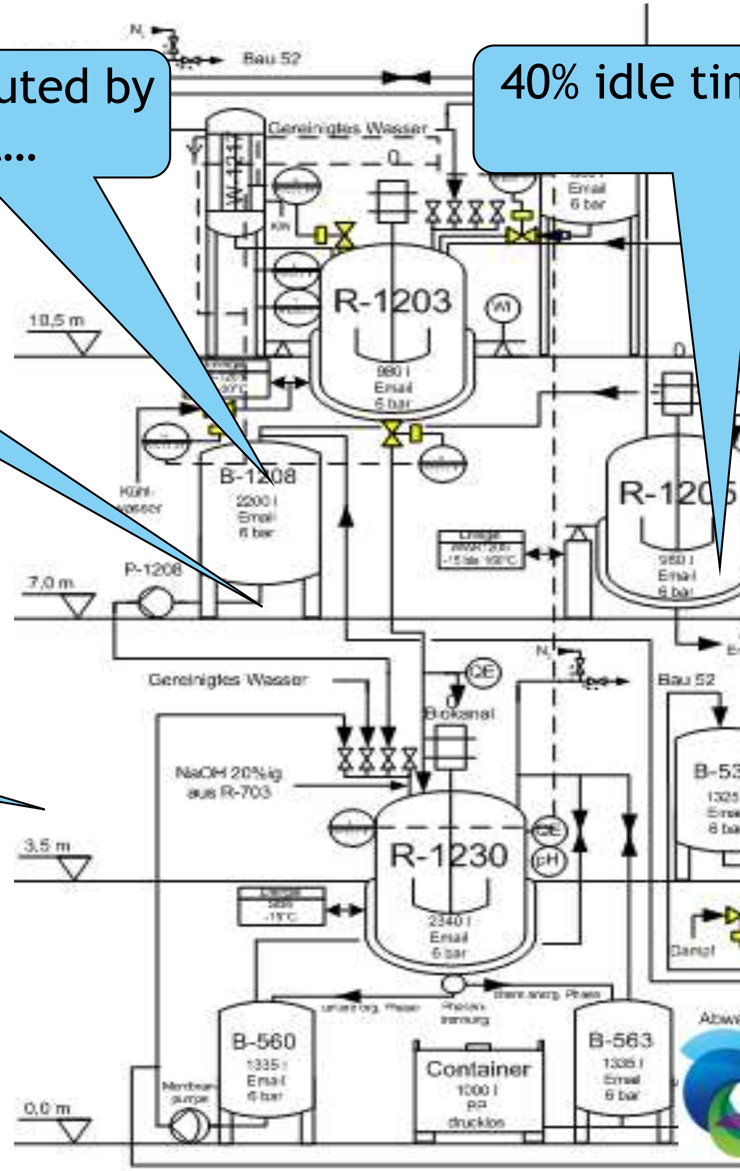
…slowly pumped into reactor

Reagents diluted by solvent…

40% idle time

…heavy cooling

Below maximum capacity



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A6, July 11, 2009, 11:40, Villefranche

Could carry 9 people at 1l/100km/ person

Could deliver 20to "just in time"

Could do 1,5 cars / sec

Could do 180km/h

would consume 4l/100km

Sustainable? Green?

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Process intensification - a different approach to synthesis

From...

Which chemicals may I use?

How do I tailor my synthesis
into my plant?

How do I control my plant
to deliver constant quality?

How do I analyze my product ?

To...

Which route would be most effective?

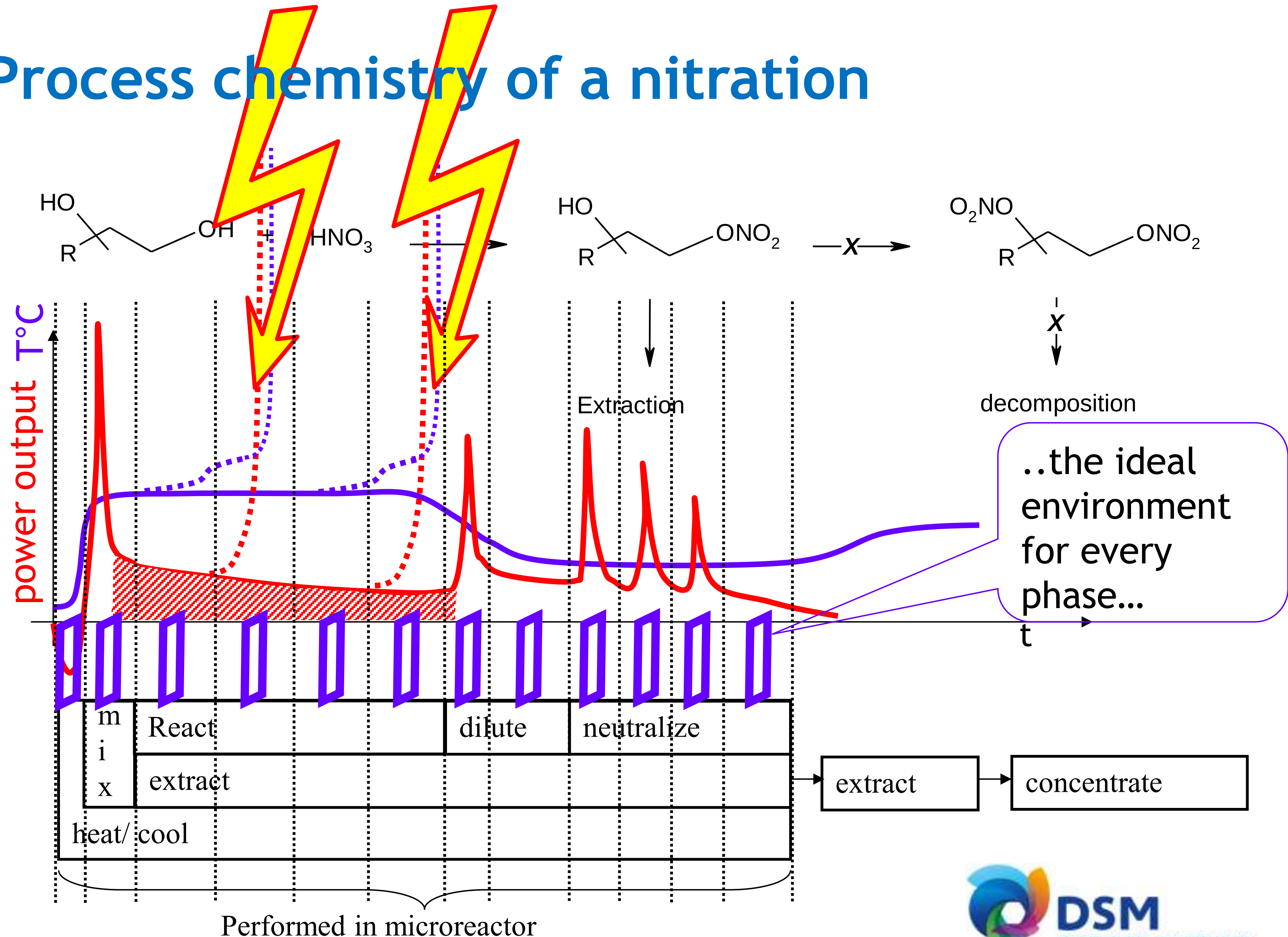
Which sequence of conditions
will make my synthesis perform best?

Which plant setup will deliver
quality by design?

How will I improve my process?

Performing a reaction in flow mode allows us to specifically meet its needs.
This improves yield, saves energy, time and space.

Process chemistry of a nitration



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Development steps of nitration process

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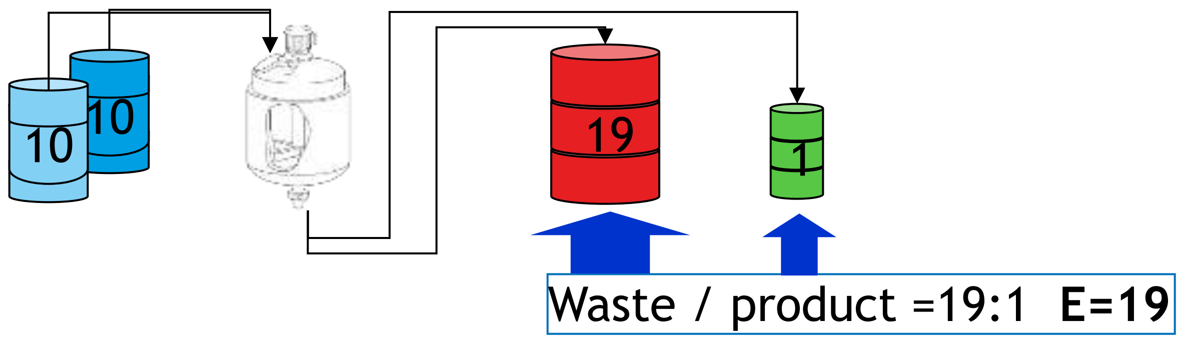
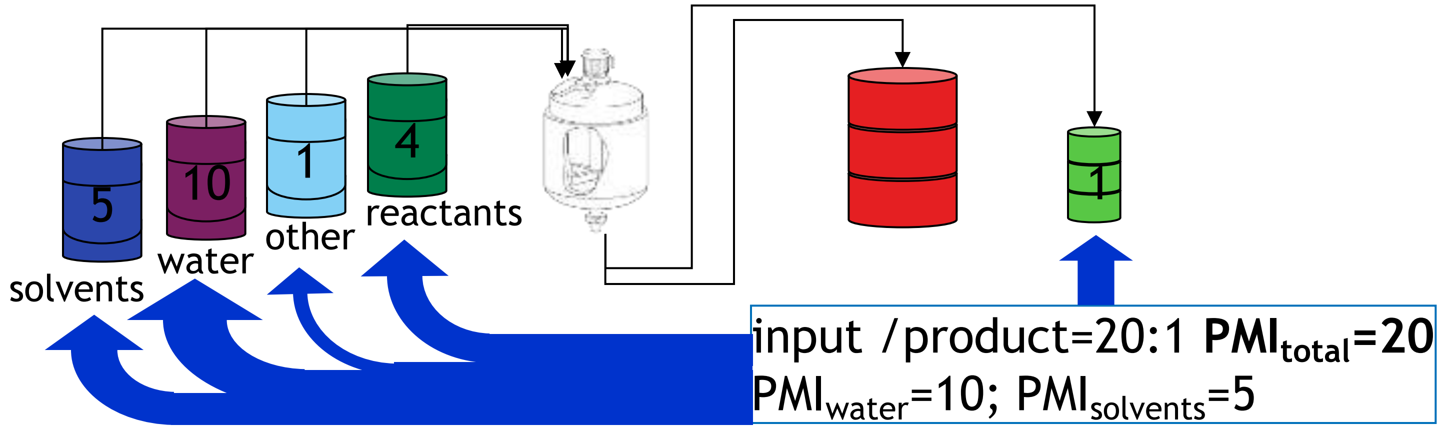
How green is green? Metrics

E-factor ("environmental factor"): how much waste is produced per kg of product?



PMI ("process mass intensity"): more detailed, relates product output to chemicals input



See Chapter "Green Engineering in the Pharmaceutical Industry" in "Green Techniques for Organic Synthesis and Medicinal Chemistry" , Wiley & Sons, 2012.

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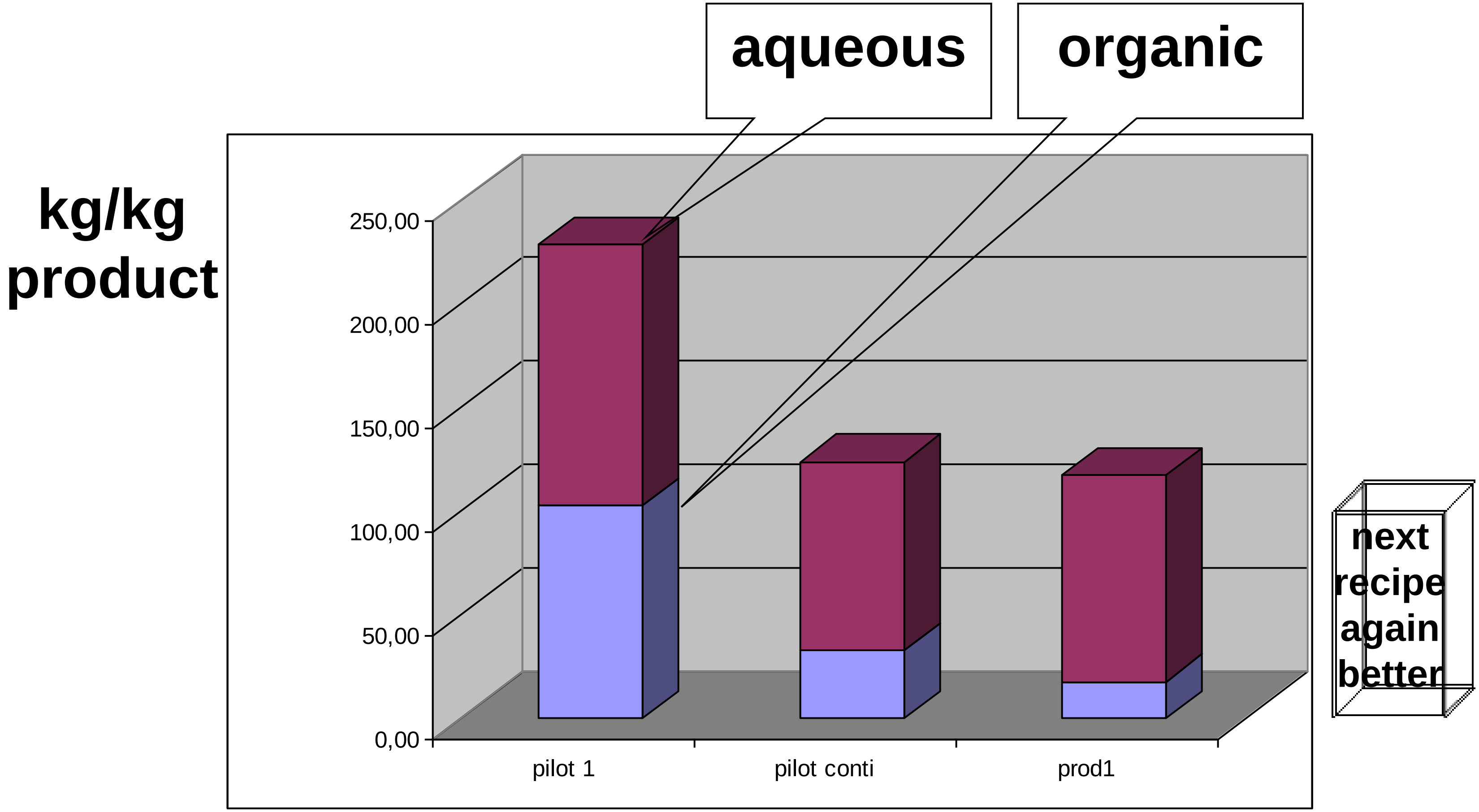
Reduction of PMI in nitration process:



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variability

- ...of chemistry applicable on full scale production: a continuous expansion of the chemistry and biochemistry toolbox by using
- "lab reagents" produced and used in situ on demand in a continuous plant (phosgene, diazo compounds, acroleine, diimine..)
- demanding process conditions (pressure; temperature; time [sec])
- "lab" separation technologies: SFC; continuous multi-step extraction;

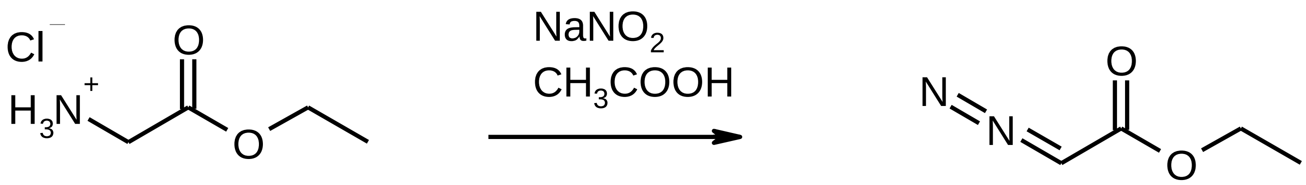
we have developed the following elements flow syntheses on various scales:

- continuous analytics
- cation chemistry
- generation of diazomethane
- low temp metallation
- azidation
- chlorination
- hydrogenation
- nanoparticle formation
- ethyl diazoacetate and carbene reaction

} avoid process changes during scale-up

Ethyl diazoacetate & carbene reaction

The synthesis of ethyl diazoacetate is seemingly simple:



ethyl aminoacetate *HCl
(glycine ethyl ester *HCl)
103.12
C4H9NO2 * HCl

ethyl diazoacetate
114.12
C4H6N2O2

"To a cooled acidic solution of glycine ethyl ester hydrochloride add sodium nitrite solution and extract the product with an organic solvent".

Pure EDA is dangerous:

- Start of decomposition at 65˚C
- Energy of decomposition 1605 J/g
- Positive result in „drop hammer" test" at 29,4 J

Do not transport
Do not store
No mineral acids
No metal ions

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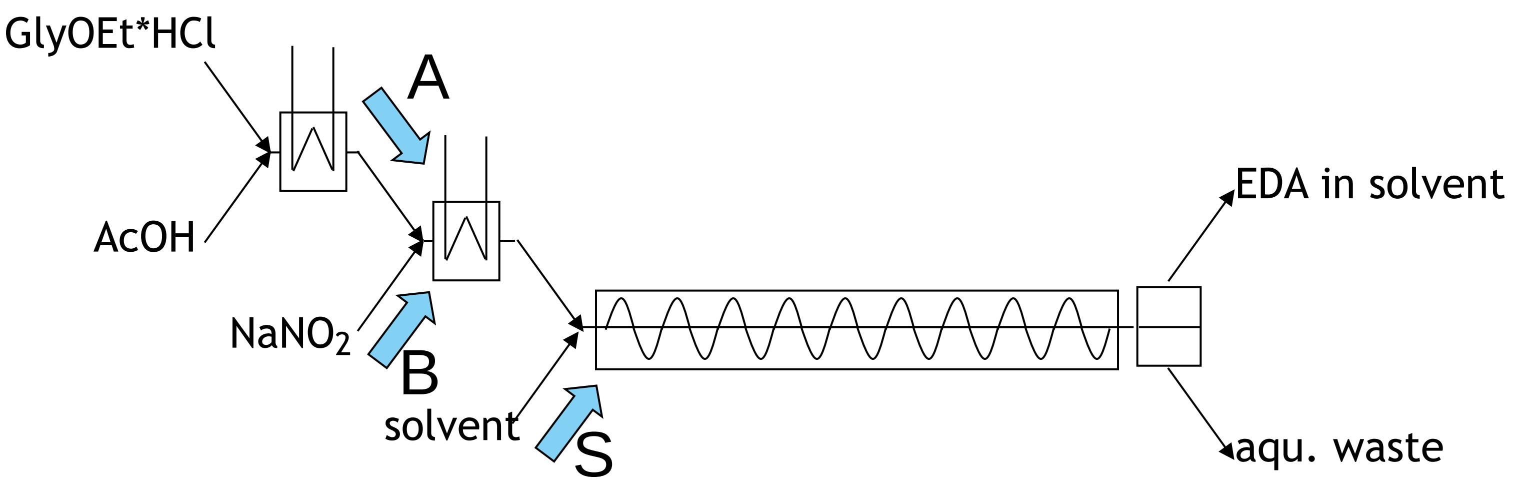
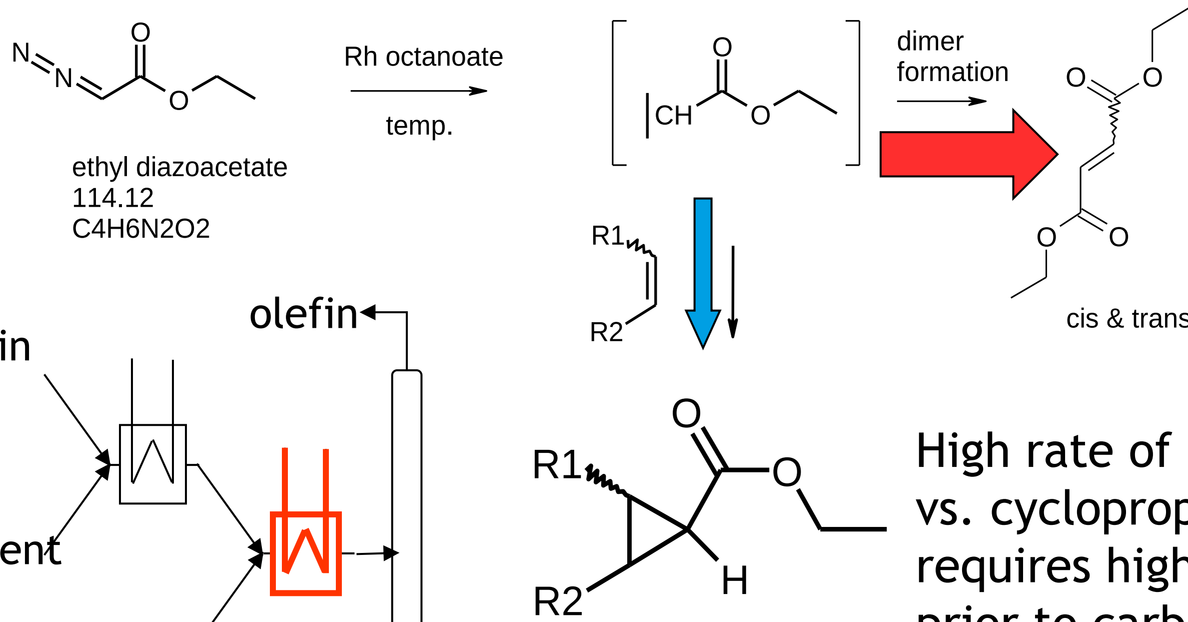
Ethyl diazoacetate: flow equivalent of lab recipe:

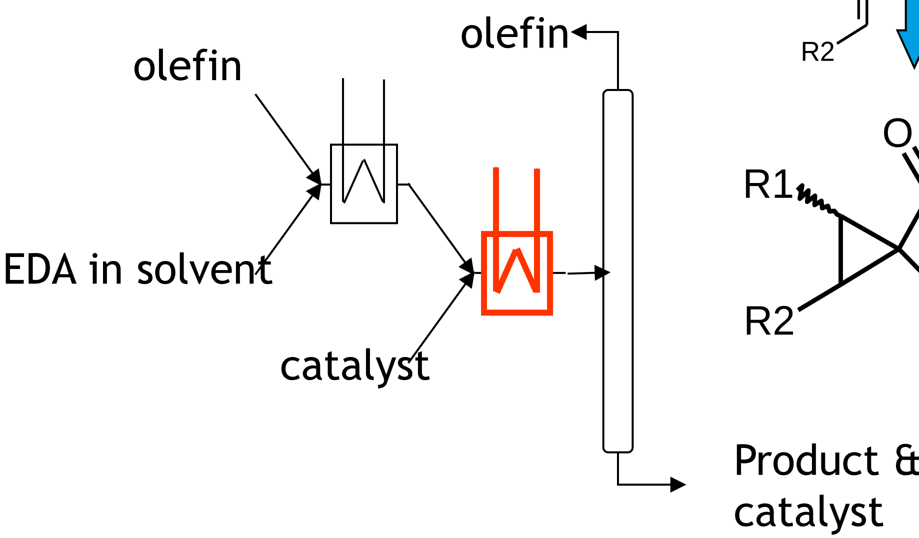


“To a cooled acidic solution of glycine ethyl ester hydrochloride =:**A**
add sodium nitrite solution =:**B**
and extract the product with an organic solvent” =:**S.**

Further reaction of ethyl diazoacetate

Carbene formation & cyclopropanation of unreactive olefin:

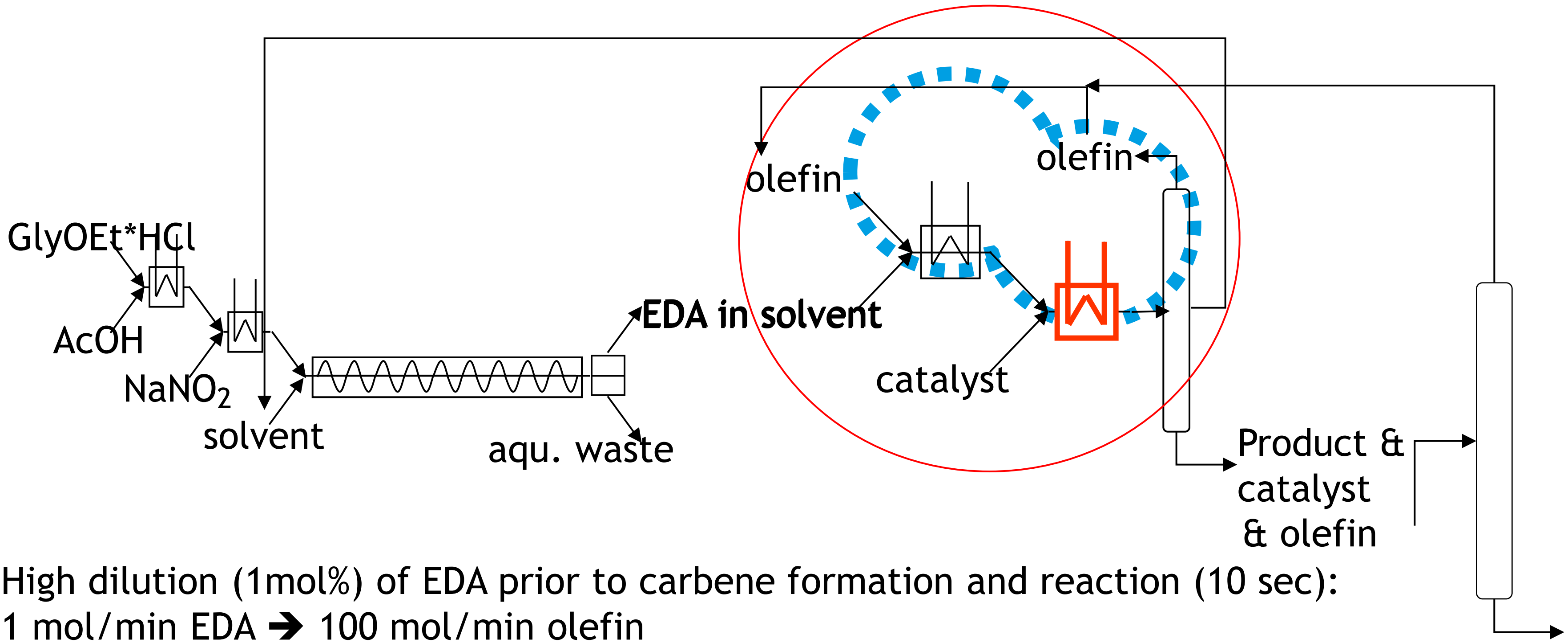




High rate of dimer formation vs. cyclopropanation requires high excess of olefin prior to carbene formation

“dilute EDA solution using the olefin
add carbene forming catalyst
and heat up;
cool after reaction”.

Combine plants…

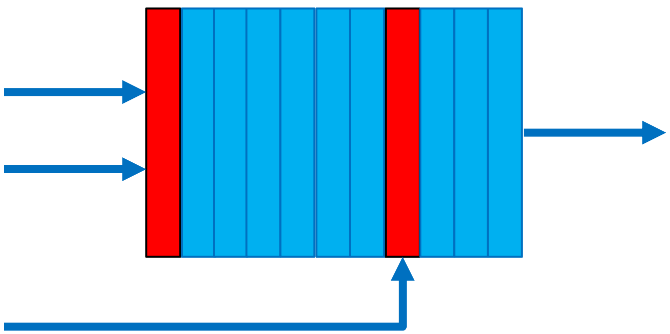


High dilution (1mol%) of EDA prior to carbene formation and reaction (10 sec):
1 mol/min EDA ➔ 100 mol/min olefin
➔ ~ 500 kg/h distilled; reactor hold-up: <2kg

flexibility

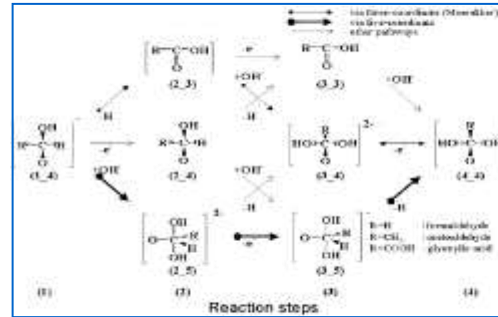
Key factors:

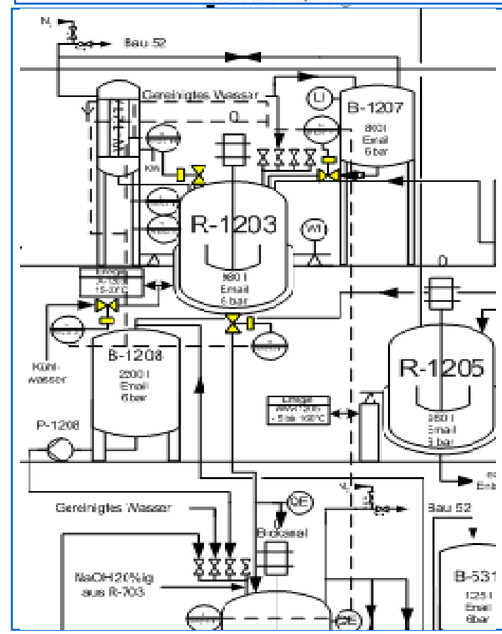
- minimize the cost of goods and the total installed cost
- further accelerate scheduling for design, build and construction
- make facilities more flexible and adaptable for a range of products by
  - modularization of construction and process implementation
  - use of disposables



Hurdles to implementation 1

Design and scale-up of intensified processes: a multidisciplinary effort …and a perceived lack of adequately educated job candidates.



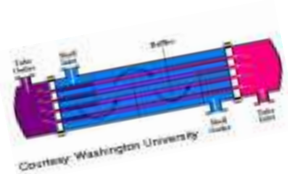


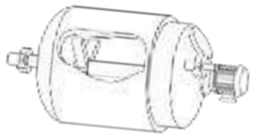
- reaction order & kinetics
- A➔P; 2A➔P; A+B➔P

- Reaction rate
- energy demand/release
- Rate=f(c,T); P=ΔH_R*Rate

- reactor performance
- U (heat transfer); t_{mix}; Re;..

- reactor features:
- dimensions, temp / pressure resistance
- order of reactant addition





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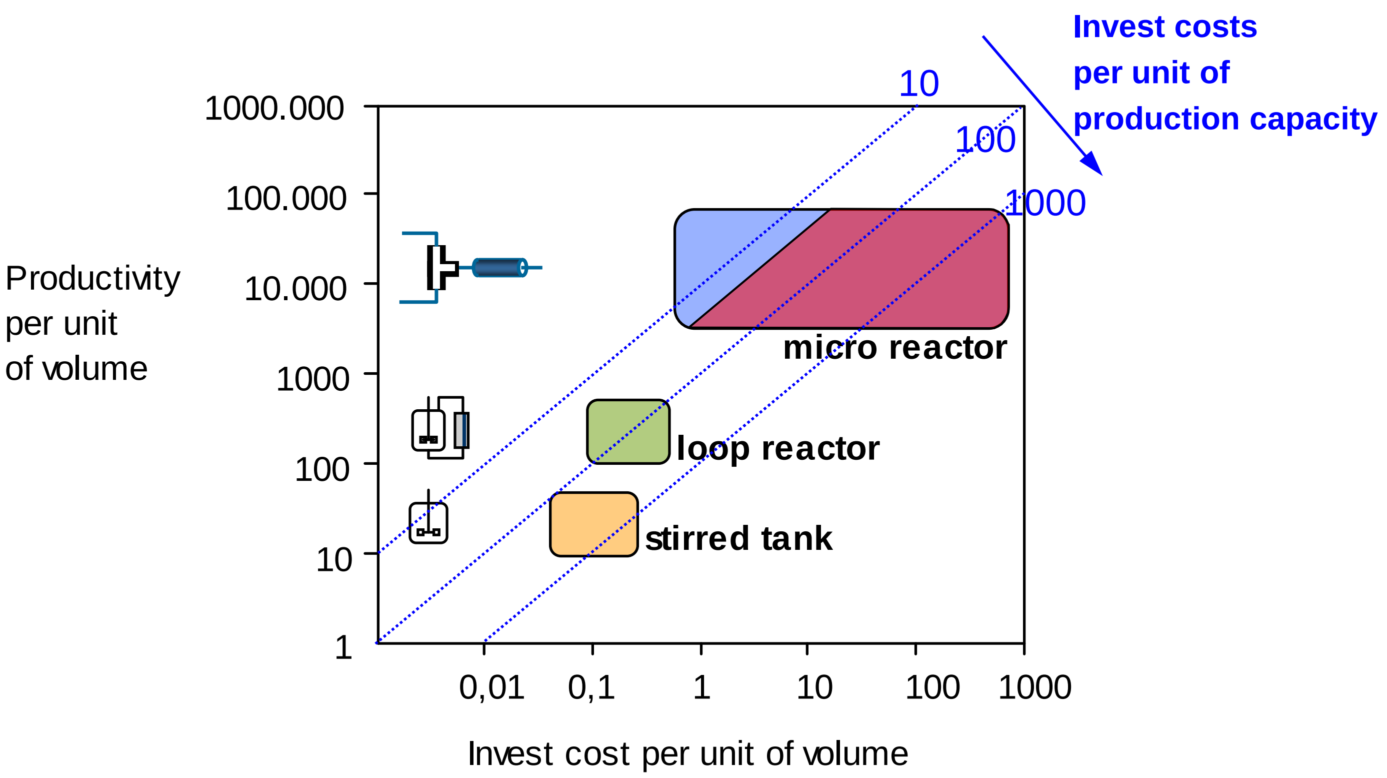
Hurdles to implementation 2

There is an uncertainty about scale-up concepts from lab to pilot and production. Simply take costs per capacity:



Teaming up with the right supplier is essential

(material+method+cost)

Choice of the right construction material

Influence of construction material and method on manufacturing cost

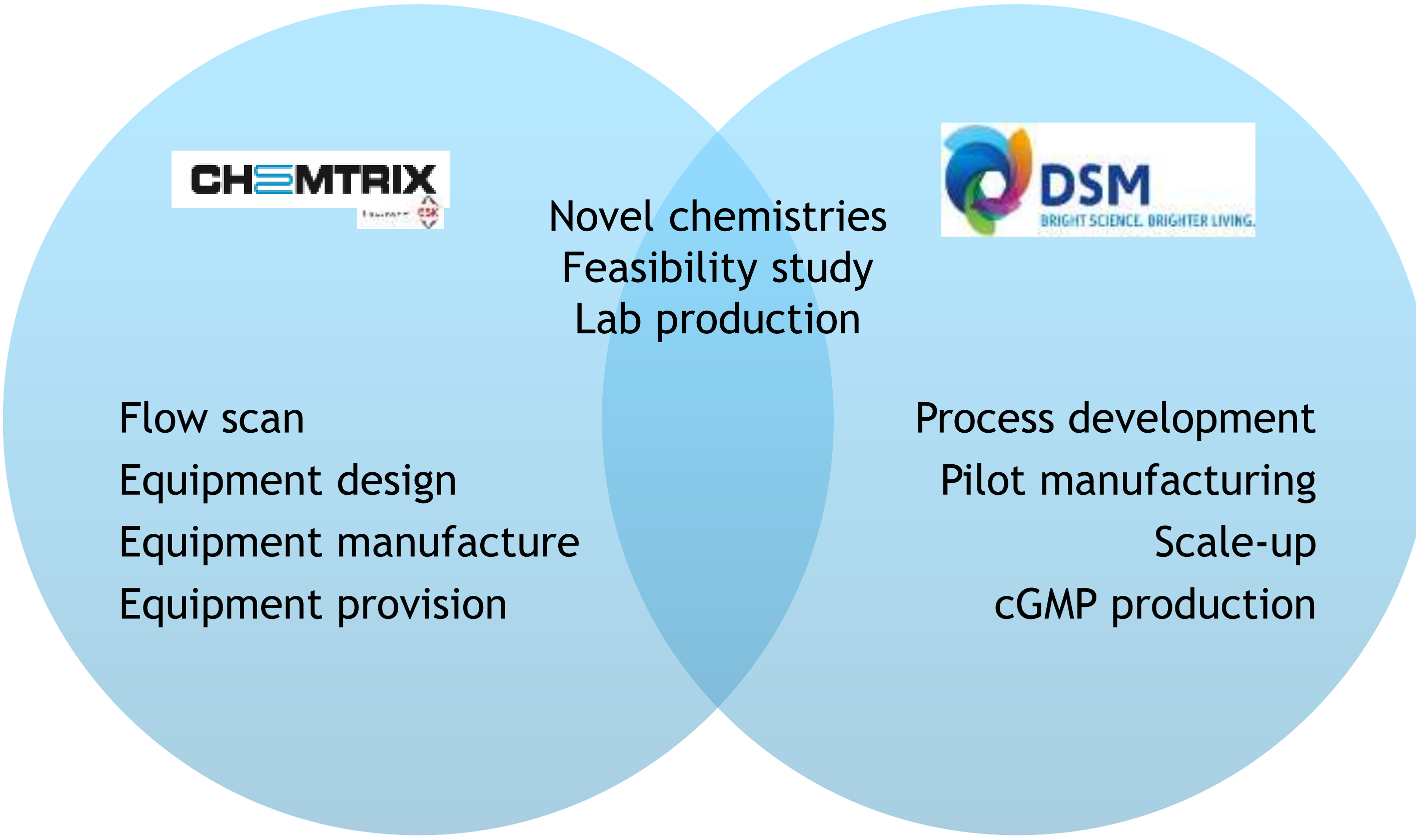
	polymer	glass	ceramic	metal
<u>Construction material</u>				
- Corrosion problems	org.solvent	base	none	acids, halogens
- Heat conductivity	low	medium	high	high
- Mechanical strength	low	medium	medium	high

<u>Construction methods</u>

- Channel shaping: machining, laser, etching, sandblasting, punching
- Paralellization: multiple channels per sheet, stacking of sheets
- Assembly: diffusion bonding, clamping

Construction material and method of processing have a big influence on manufacturing

DSM / Chemtrix Alliance: Value Proposition



TOGETHER we address ALL your Flow Chemistry needs, from conception to delivery

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Chemtrix Flow Chemistry Equipment

Scalability & System Flexibility from Lab to Production

DISCOVERY

Labtrix®

(μg to mg's)

-20 to 195 °C

Turnkey system

- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

DEVELOPMENT

KiloFlow®

(g to kg's)

-15 to 150 °C

Turnkey system

- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

PRODUCTION

Plantrix® Reactor

(kg to ton's)

-30 to 200 °C

Turnkey system

(with partner)

- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

Status and activities of large fine chemicals and pharmaceutical producers

- The vast majority of large fine chemicals and pharmaceutical producers have implemented or consider implementing intensified & continuous flow processes.

- Most have done so in an opportunistic way (immediate advantage), for the following communicated reasons:
  - Speed up development phases
    - Avoid process changes during development
    - Speed up product supply
  - Improve on environmental footprint
  - Decrease investment for capacity build-up or expansion
  - De-bottleneck existing processes to increase throughput.

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Conclusions

- Continuous processing in the manufacture of fine chemicals is moving from embryonic to maturity.

- It simplifies QbD solutions that meet authorities' guidelines
- It helps companies to meet their sustainability / greenness goals

- We consider intensified processes to:
  - Shorten development times
  - Improve productivity and safety
  - meet quality goals
  - meet sustainability goals

Thank you

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