

# Sustainable Production of Pharmaceutical Intermediates and API's



— *the* challenge for the next decade

Ronald Gebhard, PhD  
Director of R&D

# Content

- **The pharma industry:**  
Actions to increase awareness of green processes
- **Sustainability at DSM:**  
Corporate vision
- **Examples of sustainable production processes:**  
Integration of technologies is key!

# Challenge for the pharmaceutical industry: Decrease amount of material used to make a drug



## Process Mass Intensity Metric (PMI) in Context



Industry	E-factor	Annual Production tonnes	Total Waste tpa	No of transformations	Years of development
Oil Refining	ca. 0.1	$10^6 - 10^8$	10 million	Separations	100+
Bulk Chemicals	<1 to 5	$10^4 - 10^6$	5 million	1-2	10 – 50
Fine Chemicals	5 to >50	$10^2 - 10^4$	0.5 million	3-4	4 - 7
<b>Pharmaceuticals</b>	<b>25 to &gt;100</b>	<b><math>10 - 10^3</math></b>	<b>0.1 million</b>	<b>6+</b>	<b>3 - 5</b>

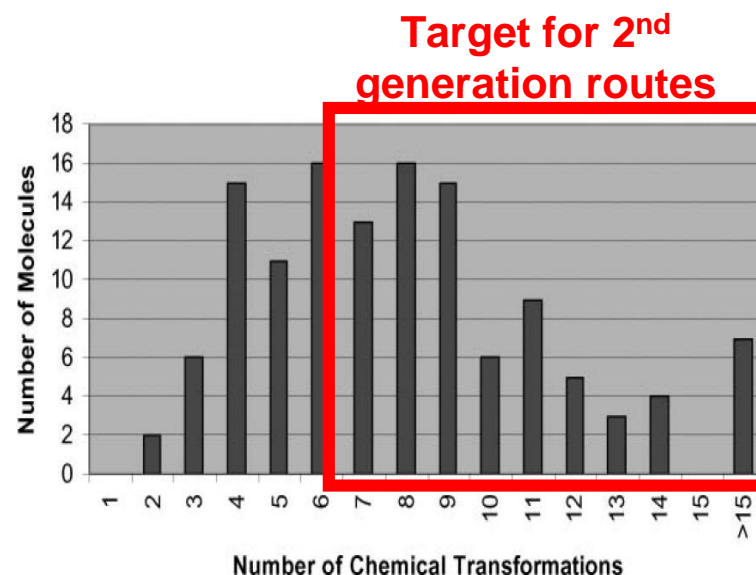
Total Waste tpa = Highest E-Factor x Largest Annual Production Volume

The last two columns were estimated for illustrative and discussion purposes only. These were not taken from a peer-reviewed publication. Years of development is meant to illustrate the amount of time a process has been able to be optimized.

# Pharma molecules get increasingly complex: *Increased need to change the process*

## Complexity increases

- Complexity of structures increases to create high target specificity
- Often brand new (not yet fully developed) technologies and reagents are used to create molecular specificity
- Protection/deprotection and classical resolution are frequently used:
  - Especially in 1st generation processes
- Number of steps/molecule is increasing from 7-10 in branded molecules to often > 15 in pipeline molecules



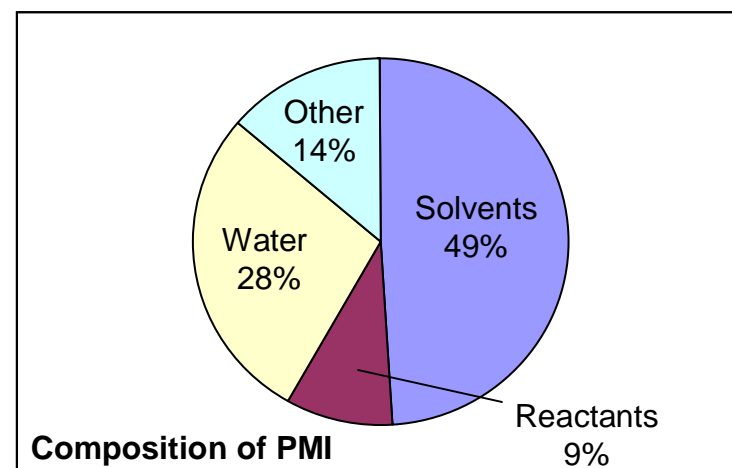
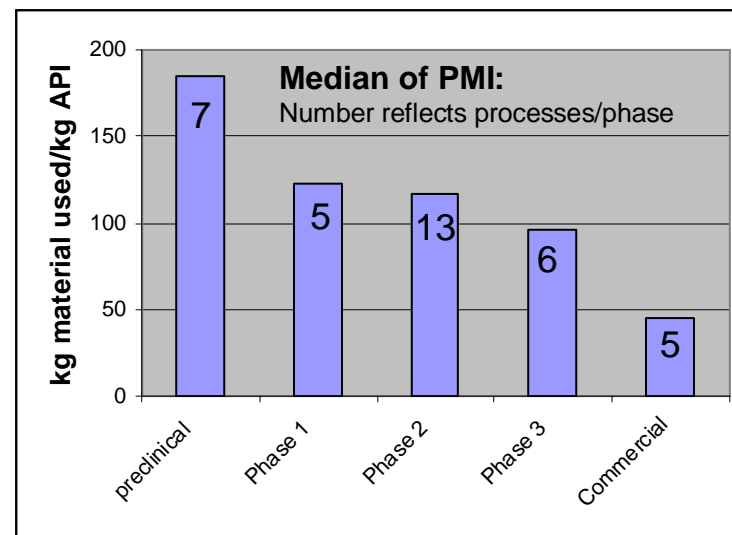
*Most first generation routes are linear and mainly consist of robust proven technology on lab-scale; opportunity for convergent or shorter 2<sup>nd</sup> generation routes*

Sources: *Org.Biomol.Chem.*, 2006, 4, 2337-2347; DSM data

# Process mass intensity by development phase: *Focus already in R&D can improve PMI figures during the development phase*

- PMI clearly decreases during the development process
- Solvents and water contribute up to 80% of the process mass intensity
- Early focus in research is needed to reduce the use and hazard of solvents and reagents

Data source: ACS Green Chemistry Institute® Pharmaceutical Roundtable



# The ACS Green Chemistry Institute<sup>®</sup> Pharmaceutical Roundtable: *A joint responsibility towards sustainable processes in pharma*

- In 2005, Pfizer, Lilly and Merck founded the Roundtable under the ACS Green Chemistry Institute<sup>®</sup>, followed by AstraZeneca, Schering-Plough, Johnson & Johnson and GlaxoSmithKline



- Objectives:
  - Encourage innovation while integrating green chemistry and engineering into drug discovery, development and manufacturing
  - Inform & influence the research agenda
  - Define and deliver tools for innovation
  - Educate leaders (current and future scientists)
  - Collaborate globally
- Today, 10 Pharma companies are members and two suppliers have associate membership status

# Requirements for suppliers to pharma

Increased pharma focus on sustainable process design, poses a challenge to the CMO industry:

“Meet or (*preferably*) be better than pharma in greening pharma processes.”

Required:

- A corporate culture setting the boundaries
- A track record in sustainable manufacturing
- A strategy, and resources, to work at the forefront of green process R&D

# Facts on DSM: Company Profile 2008

## Global Top 30 chemical industry

- Net sales €9,3 billion
- Net profit €577 million



World Business Council for  
Sustainable Development



## 23,500 employees

- ~2000 in R&D
- 200 locations on 5 continents



## No 1. Dow Jones Sustainability Index

- 2003, **2004**, **2005**, **2006**, 2008-2009  
(European Chemical and Global Chemical)



## Strong technological toolbox:

Integrated use of organic chemistry, biotechnology, biocatalysis, process and polymer technology and material sciences



## January 2009

First non-pharma (associate) member of the ACS Green Chemistry Institute® Pharmaceutical Roundtable



**DSM Pharmaceutical Products**

Unlimited. **DSM**

# Sustainability at DSM ...

***“We cannot be successful, nor can we call ourselves successful, in a society that fails.”***

**Feike Sijbesma**  
Chairman of the Managing Board



## **All about (societal) needs:**

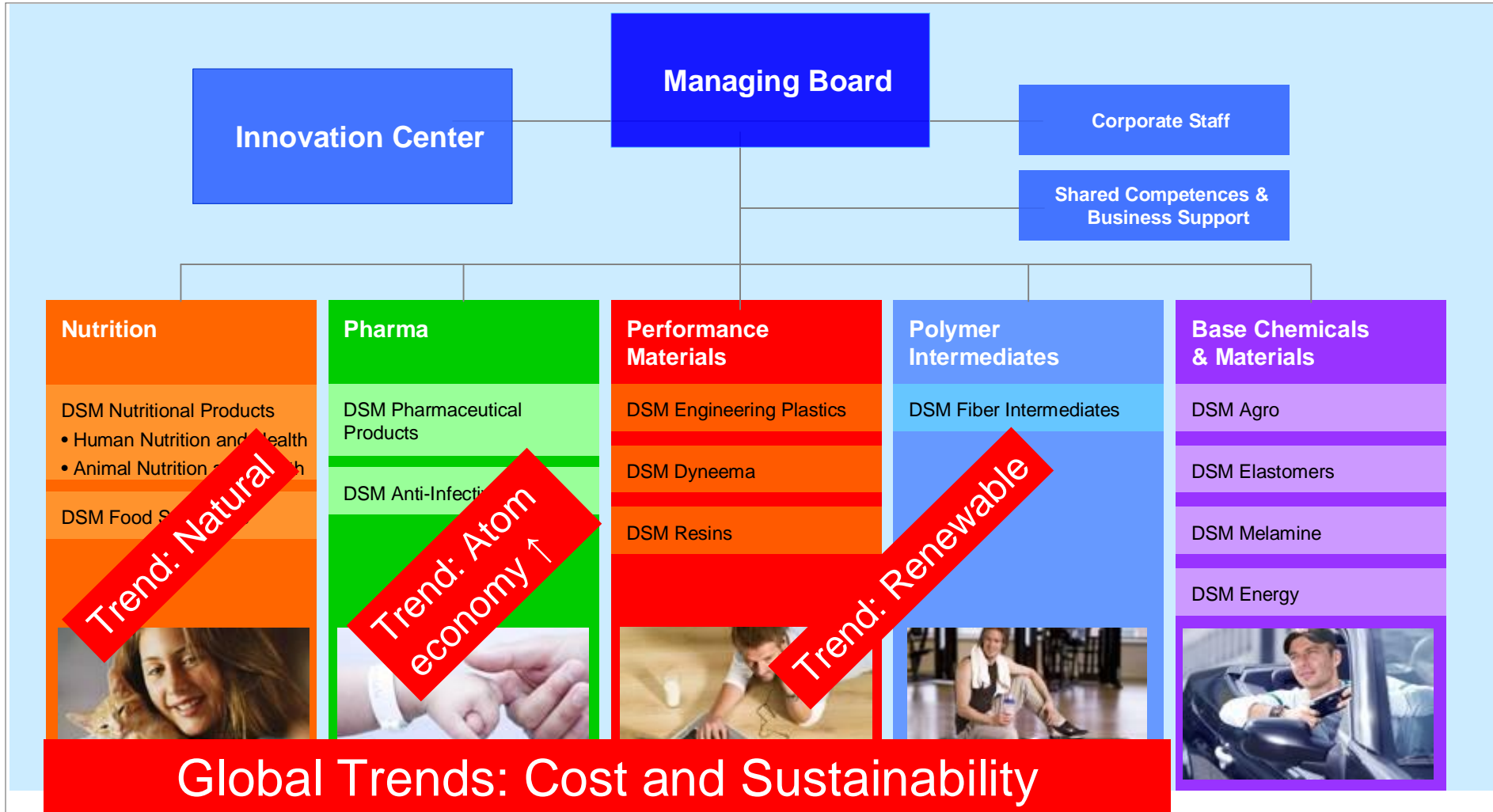
- **Recognizing the needs** – stakeholder engagement
- **Preparing to meet the needs** – DSM Sustainability strategy and processes to deliver (footprinting, PMP)
- **Fulfilling needs** – creating value propositions, mitigating risks (Product Launch, Excellerate, Product Stewardship)

# Addressing current global challenges

- The *real* issues of today's society:
  - (Alternative) energy sources
  - Climate change
  - Balanced food supply and health
- Today's issues require 21st century solutions, based on **new business models** where **sustainability and environmental relevance** go hand in hand with economic feasibility



# DSM Organizational Chart



**DSM Pharmaceutical Products**

*Unlimited.* **DSM**

# DSM's Triple approach

## DSM combines three main routes towards sustainable production of pharma chemicals:

1. Corporate SHE requirements and sustainability metrics
2. Development of sustainable technology platforms, supported by state-of-the-art tools
3. Proactive management of learning curve



Green routes for  
Vitamins  
and  
pharmaceuticals



Improving eco footprint  
throughout value chain

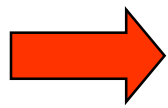
DSM Pharmaceutical Products

Unlimited. **DSM**

# DSM Corporate Requirements

## • Safety, Health and the Environment

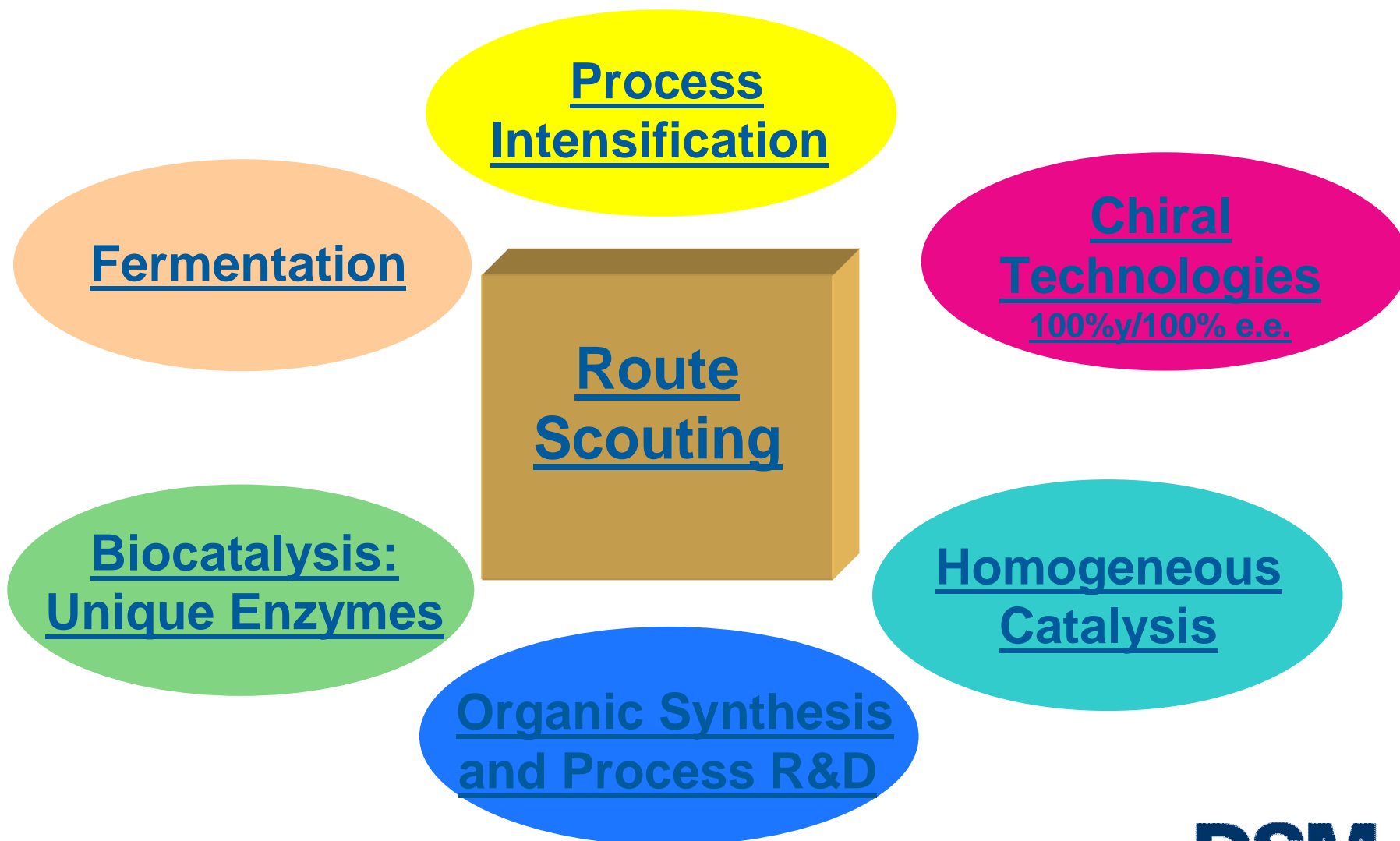
- Considerations and assessments are made to ensure that:
    - Products are developed such that the associated SHE risks are controlled and minimized for their total life-cycle
    - Production processes and products are chosen such that the use of raw materials and energy is minimized
- 



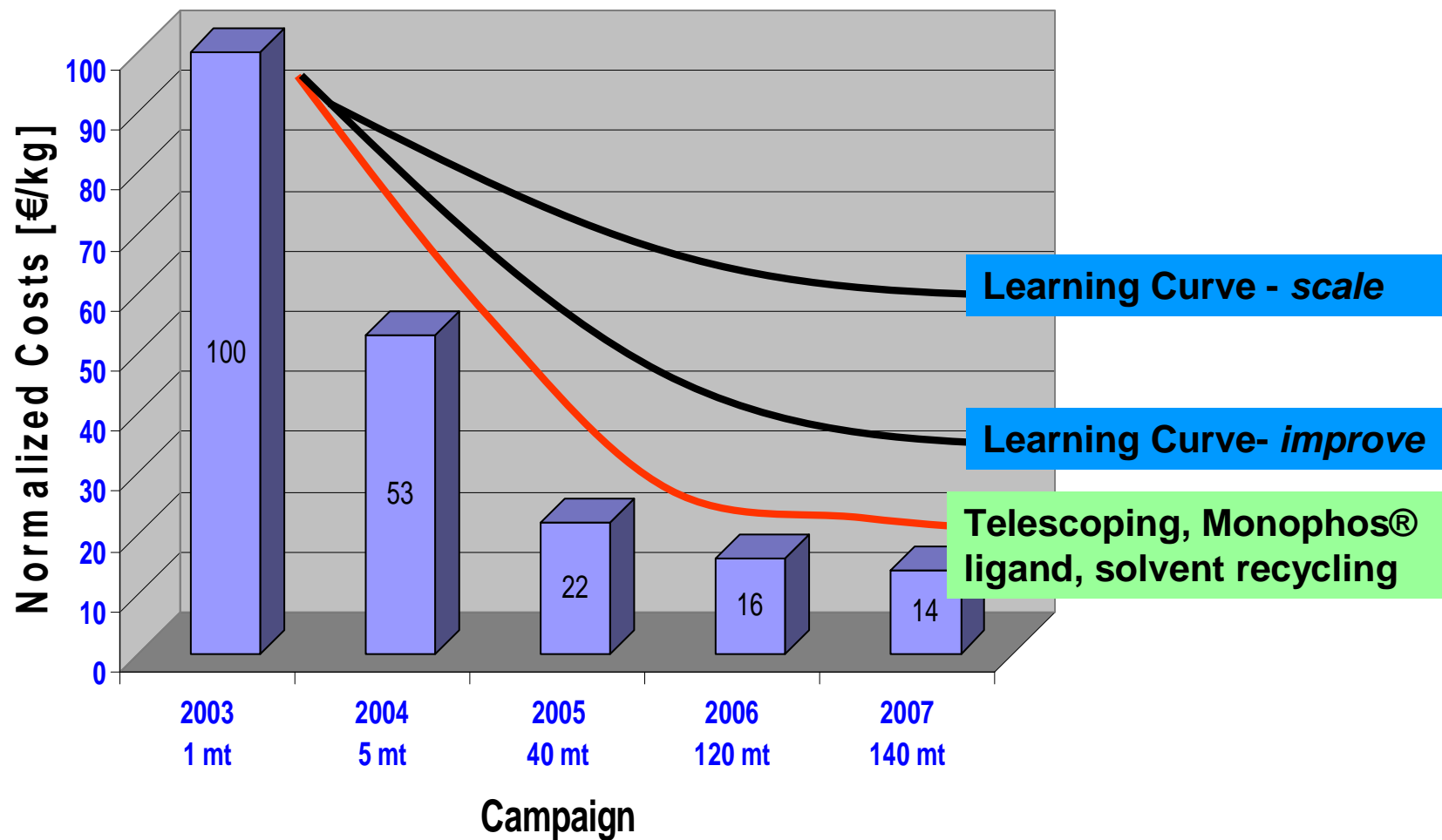
For pharma CMO, current activities focus on developing an “LCA light” tool for pharma intermediates!



# Access to an integrated set of modern technologies is crucial for sustainable route design



# Proactive management of a learning curve



# Examples of sustainable Proces Development at DSM

1. Biocatalysis: an indispensable tool in green process design;  
examples:
  - *Beta lactam cephalixin*
  - *Development of recombinant Pig Liver Esterase (PharmaPLE™) to replace a classical resolution*
2. Combining Biocatalysis and Homogenous Catalysis shortcuts synthesis of a pharma intermediate
3. Hydrogenation Technology: *homo and hetero can do the job*
4. Process Intensification using micro reactor technology

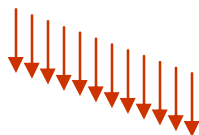
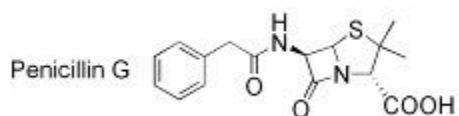
# DSM Process for the antibiotic Cephalexin (1)

## *Fermentation of a Non-Natural Compound*

### 'Old Route'

Sugar

Traditional  
Fermentation

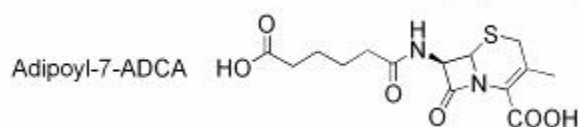


13 chemical steps

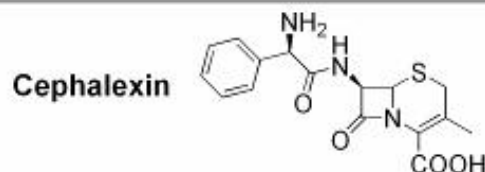
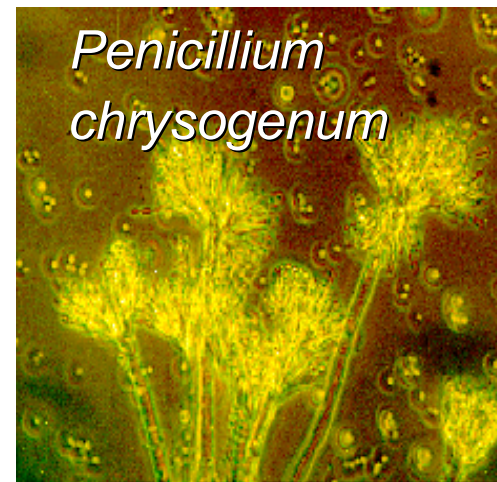
### New Route

Sugar

Metabolic  
Engineering

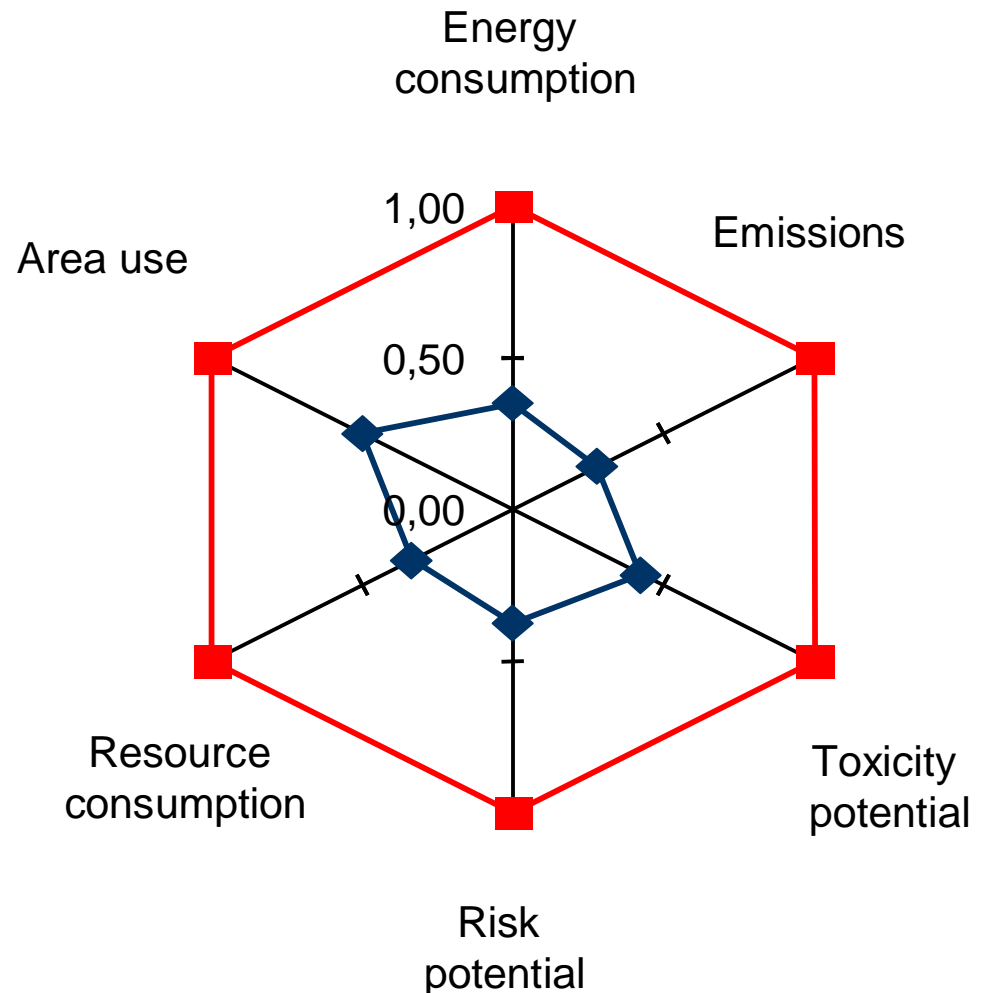


2 enzymatic steps



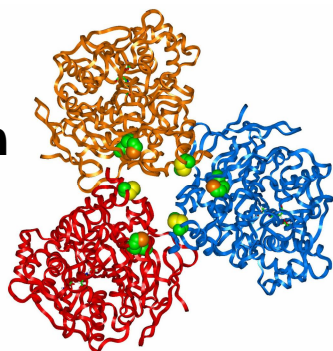
# Life cycle analysis of DSM Cephalexin process

- Life cycle analysis by the Öko Institute
- Old **complex** chemical route vs. **white biotech** route

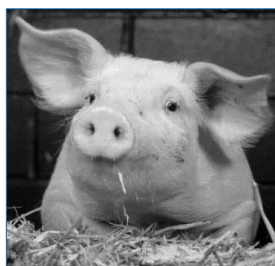


# Recent example: **Non-animal derived** PharmaPLE™ enables enzymatic resolutions at multi-ton scale

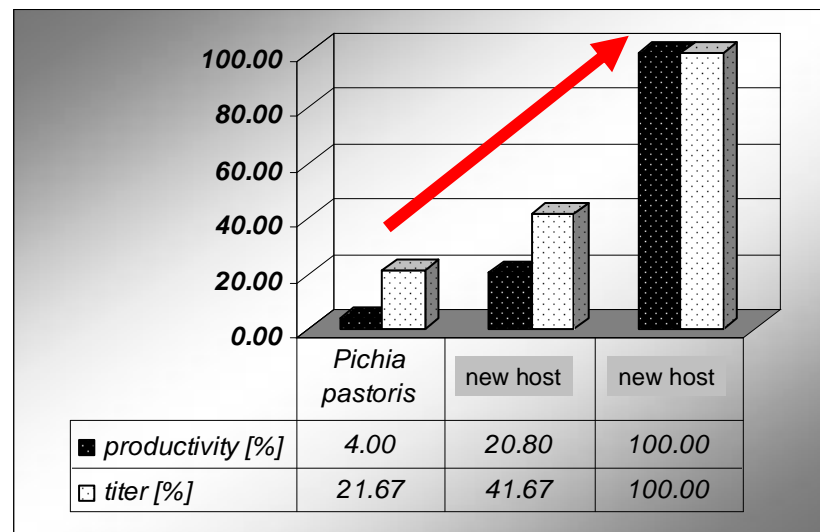
Pig Liver Esterase: one of the most versatile enzymes in organic synthesis, but.....



....animal origin hampers use for food/feed and pharma.



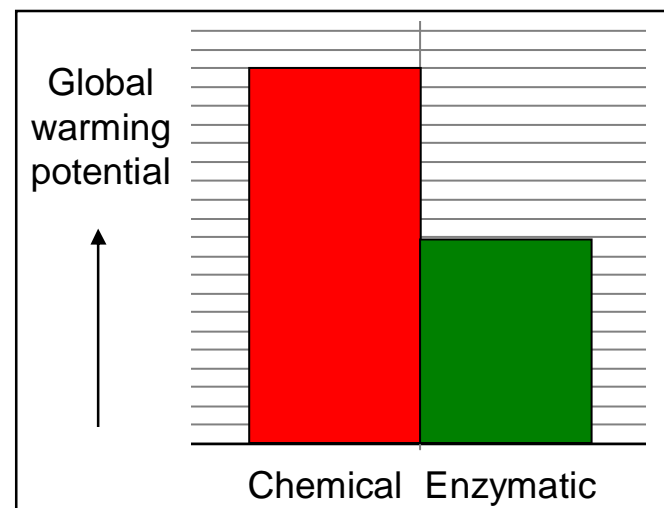
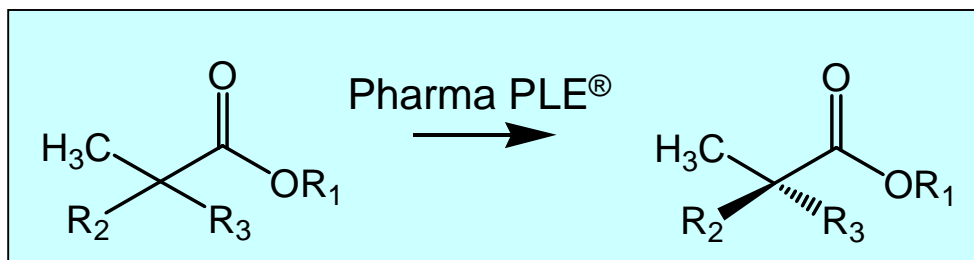
Huge improvement was obtained by specific host design



DSM has exclusive access to **non-animal derived** pig liver esterases!  
And we have scaled an applied it at multi-ton scale!

# Enzymatic resolutions generally outperform classical resolutions in carbon footprint

- **1<sup>st</sup> generation: diastereomeric resolution of a racemic mixture of a pharmaceutical ingredient**
  - Chemical route
  - Long throughput time
  - High equipment cost
- **2<sup>nd</sup> generation: enzymatic resolution**
  - Short throughput time
  - Lower equipment cost
  - Lower raw material consumption



# DSM is a leader in Applied Biocatalysis

Biocatalysis Platforms	Product Classes
L-Amidases	$\alpha$ -Amino acids, $\alpha$ -Hydroxy acids
D-Hydantoinase / D-Carbamoylase	$\alpha$ -Amino acids
R- and S-hydroxynitrile lyases	$\alpha$ -/ $\beta$ -Amino acids, $\alpha$ -Hydroxy acids
Ammonia lyases	$\alpha$ -Amino acids
Acyases	$\alpha$ -/ $\beta$ -Amino acids, Amines, Amino-nitriles
Lipases, Esterases	Carboxylic acids, Alcohols, Amines
Proteases	Peptides
Aldolases	1,2-Diols, Aminoalcohols, Hydroxyesters
Alcohol dehydrogenases	S and R alcohols
Epoxide hydrolases	Epoxides, 1,2-Diols
Racemases, Isomerases	Racemization
Haloperoxidases	Alcohols, Epoxides, Sulfoxides
Hydratases	$\alpha$ -/ $\beta$ -Hydroxy acids
Nitrilases	$\alpha$ -/ $\beta$ -Amino acids, $\alpha$ -Hydroxy acids
Transaminases	Chiral amines

**730 industrial processes implemented**

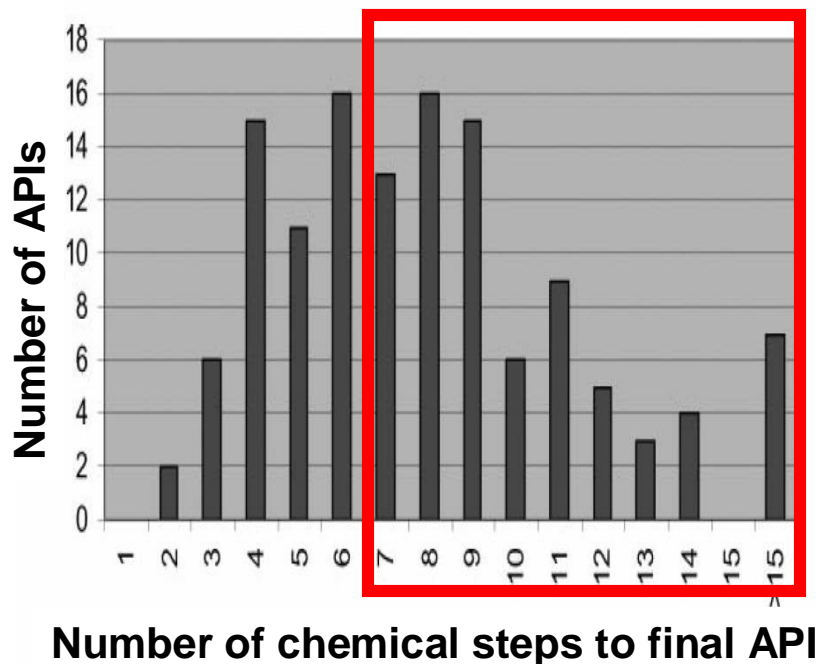
Applied at over 100kg-1000 ton scale; preparative lab-scale

DSM Pharmaceutical Products

Unlimited. **DSM**

# The best approach towards sustainable manufacturing needs more than just “bio”

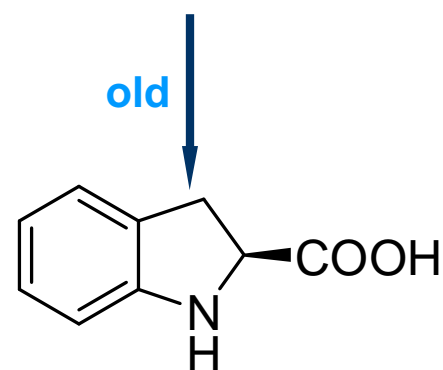
Route Scouting should involve an integrated approach of chemistry, biology and process technology



Source: *Org. Biomol. Chem.*,  
2006, 4, 2337-2347

Example: an advanced intermediate for a pharma API

7 step classical resolution



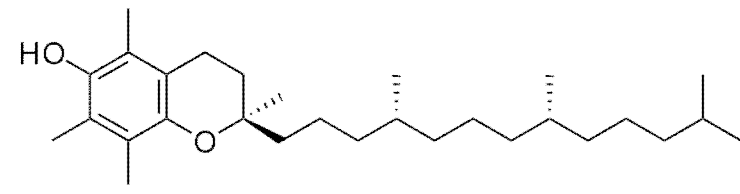
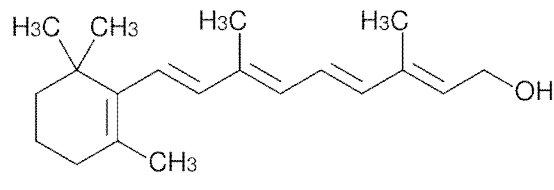
new

- 1) Enzyme
- 2) Cu catalysis

2 step process

# Catalytic hydrogenation: homo and hetero both offer sustainable solutions

- **Heterogenous Hydrogenation:** A major part of DSM's portfolio in Life Sciences is based on clean Lindlar Hydrogenation of substituted acetylenes (carotenoids, Vit A, Vit E, pharma intermediates).



- **Homogenous (Asymmetric) Hydrogenation:** Often offers 100% yield alternative to resolution processes (50% yield) and shortcut of lengthy API syntheses. DSM offers the broadest set of ligands for asymmetric hydrogenation screening and multi-ton scale-up experience

*“keep the molecule flat as long as possible”*



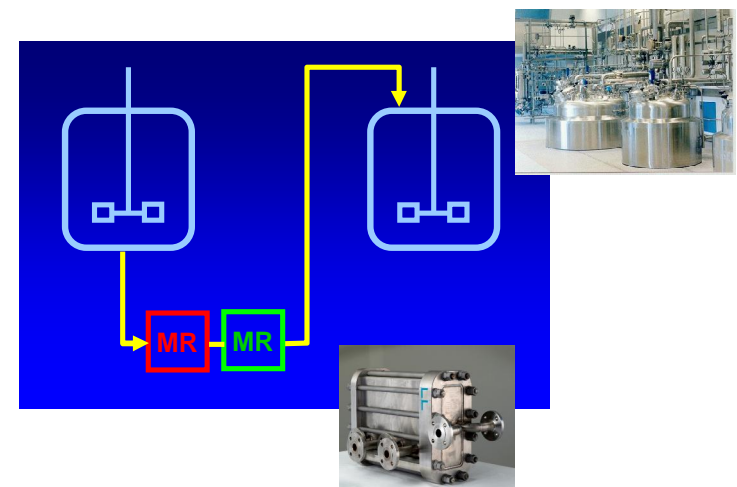
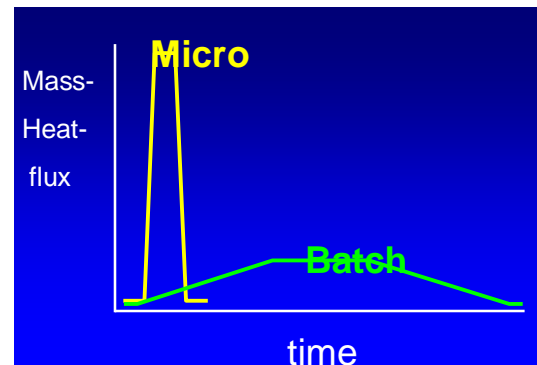
**DSM Pharmaceutical Products**

Unlimited. **DSM**

# Process intensification with micro-reactors: *An important tool towards sustainable manufacturing*

## Micro reactors enable new domains of high heat and mass transfer

- Fast heating or cooling, during short defined time
- Milliseconds mixing time
- Factor 1000 increased productivity (kg/m<sup>3</sup>h)
- Avoiding cryogenic cooling (energy)
- Modular small units enable switch from batch to continuous processing

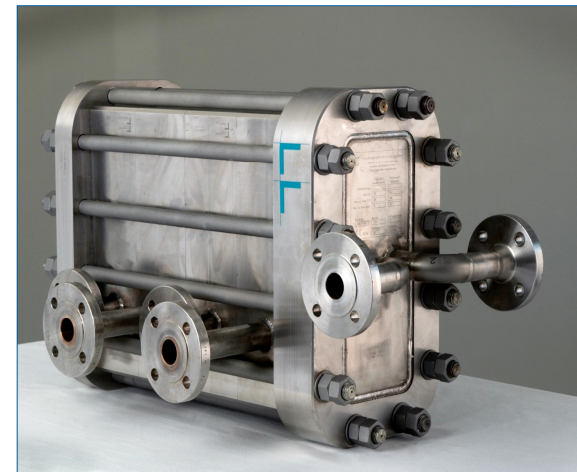


# 'Scaling up' is simply 'Numbering up'

## Scaling up a micro reactor:



10 channels: 1 kg/h

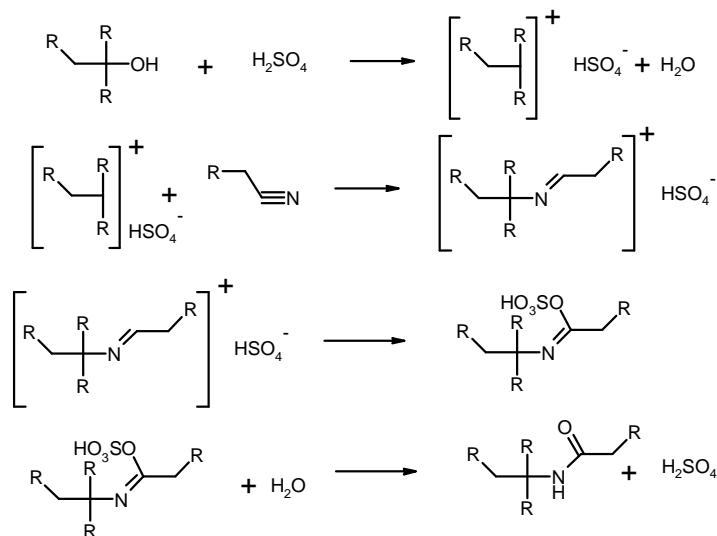


10.000 channels: 1700 kg/h

Keep the geometry equal, add channels up to the required capacity.  
Design the manifold in order to keep flow distribution equal.

# Successful multi-ton application with a higher selectivity and less waste

## Micro reactor improved selectivity of Ritter synthesis by 20%



- Less consumption of raw material and energy (purification)
- Reduced DSP efforts
- Reduced waste



# Conclusions

- Sustainable manufacturing is not a choice but a **need** in modern society; we need to create more value with less footprint
- The best road toward sustainable manufacturing relies on an integrated approach using biotech, chemistry and process technology. In R&D focus needs to be on **greening** the process
- At DSM most of the required competencies for the development of sustainable routes for pharma intermediates and API's are available in house or via **“open innovation”** with our partners

***Thank You for your attention!***

For further information:

[Ronald.Gebhard@DSM.com](mailto:Ronald.Gebhard@DSM.com)

ACS Green Chemistry Institute<sup>®</sup> Pharmaceutical Roundtable:

[www.acs.org/gcipharmaroundtable](http://www.acs.org/gcipharmaroundtable)



Disclaimer: No endorsement or approval by the ACS GCI Pharmaceutical Roundtable has been received or is in any way implied.