Implementation of New Technology in the Context of Advanced Chemical Production Processes

- The Role of R&D in the Design of Pharmaceutical Manufacturing Methods -

Hans-Jürgen Federsel

PhD, Assoc Professor, Chief Scientific Officer, EnginZyme AB, Stockholm

hans-jurgen@enginzyme.com

FORUM ASCHIMFARMA 2018

Research and Technology: the New Frontiers for Pharmaceutical Chemistry

Milan, 19th February 2018

EnginZyme

EnginZyme

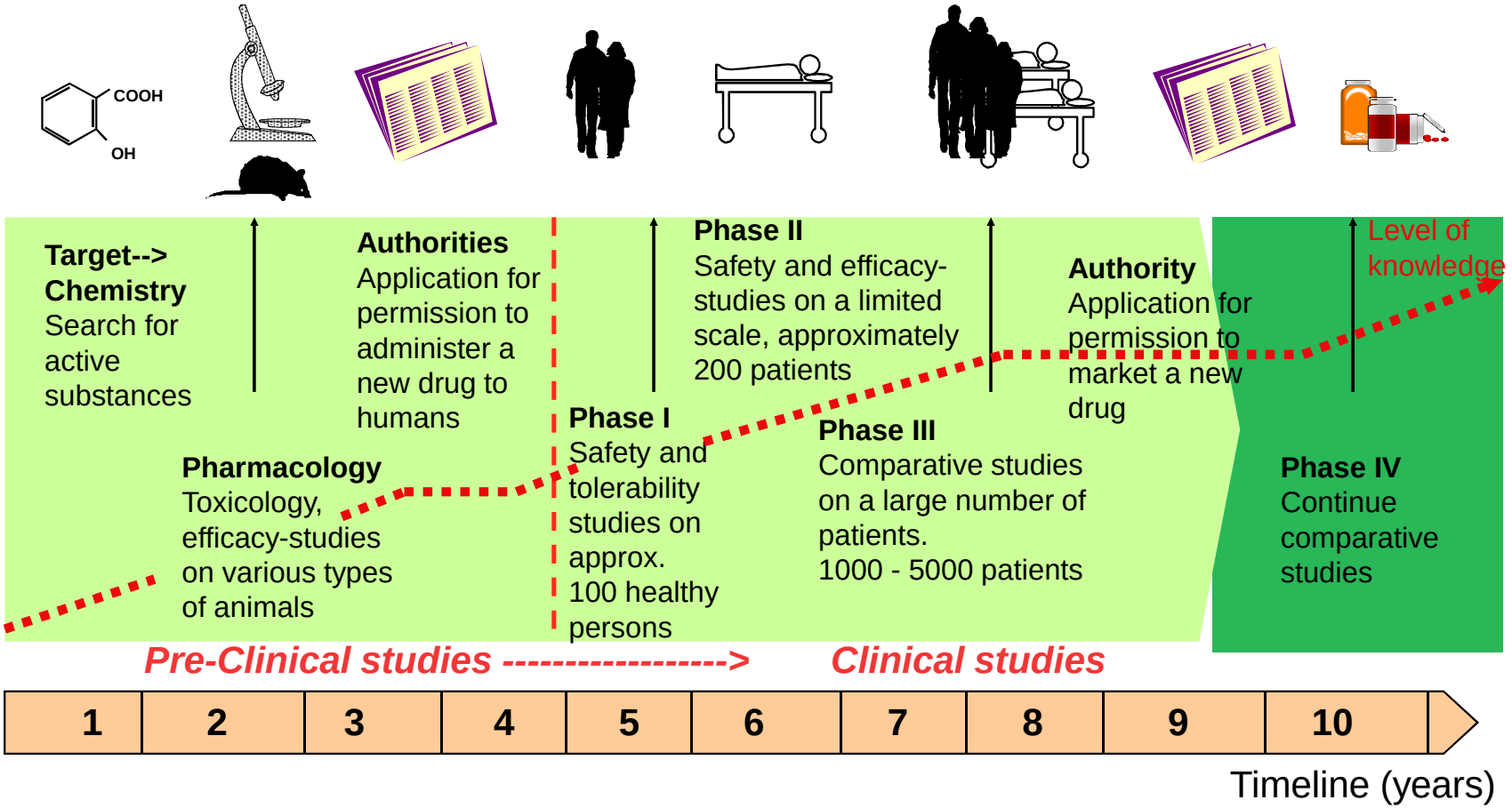
- A biotech established in 2014
- Currently located in an office/laboratory facility on the campus of the Royal Institute of Technology (KTH) in Stockholm, Sweden
- Staff number (Feb 2018): 10 people in R&D, sales, and marketing
- In a broad sense, business is about providing services in the biocatalysis area – i.e. use of enzymes for synthetic purposes
  - Unique platform operating on a solid support – porous glass beads
- Main customer focus today: pharmaceuticals, agrochemicals, flavours & fragrances, water treatment

Multiple drivers for biocatalysis

- Reduction in waste
- Atom economy
- Mild reaction conditions, hence less hazardous
- High selectivity
- Cover a wide range of chemical transformations
- Biocatalyst performance can be readily improved via enzyme evolution
- Avoid derivatives (e.g. protecting groups) – allows chemistry to be performed directly on the substrate
- Fewer process steps
- Technology is scalable
- No need for specialized equipment
- Cost benefits

In other words, the time is 100% right to step up resources and efforts in biocatalysis

From idea to registered drug

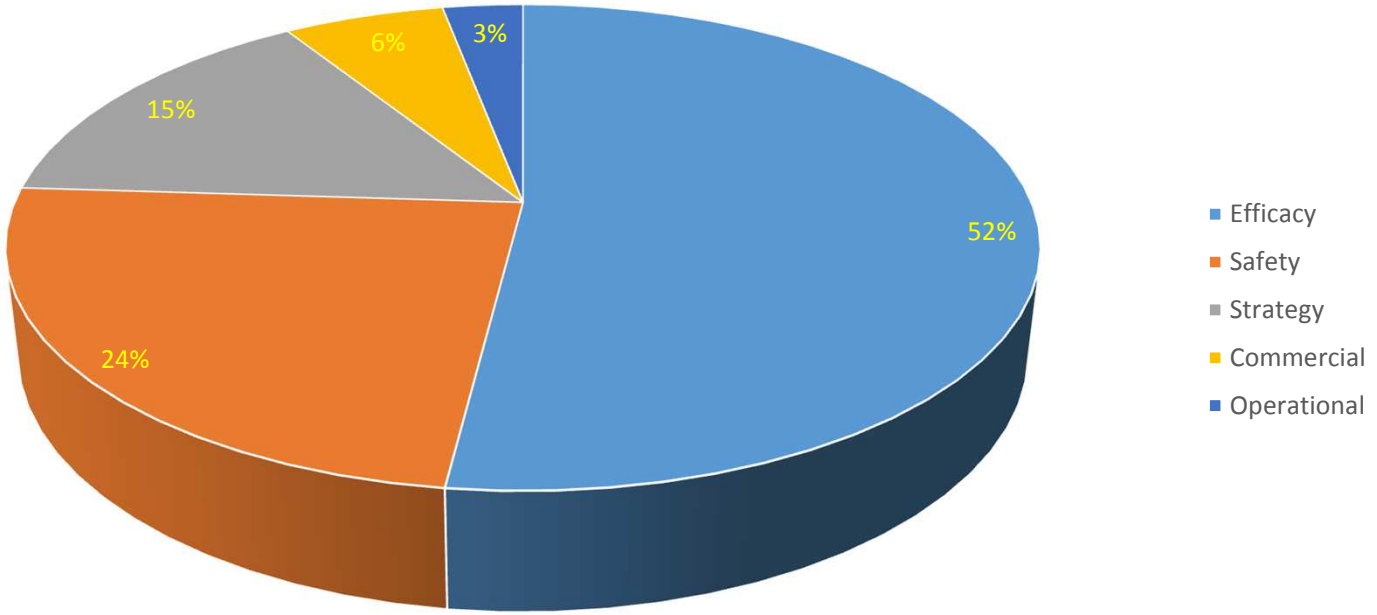


Federsel, H.-J. *Nature Rev. Drug Discov*. **2003**, *2*(8), 654-664
Federsel, H.-J. *Acc. Chem. Res*. **2009**, *42*(5), 671-680
Federsel, H.-J. *Bioorg. Med. Chem*. **2010**, *18*(16), 5775-5794

Causes for Failure (2013-2015)

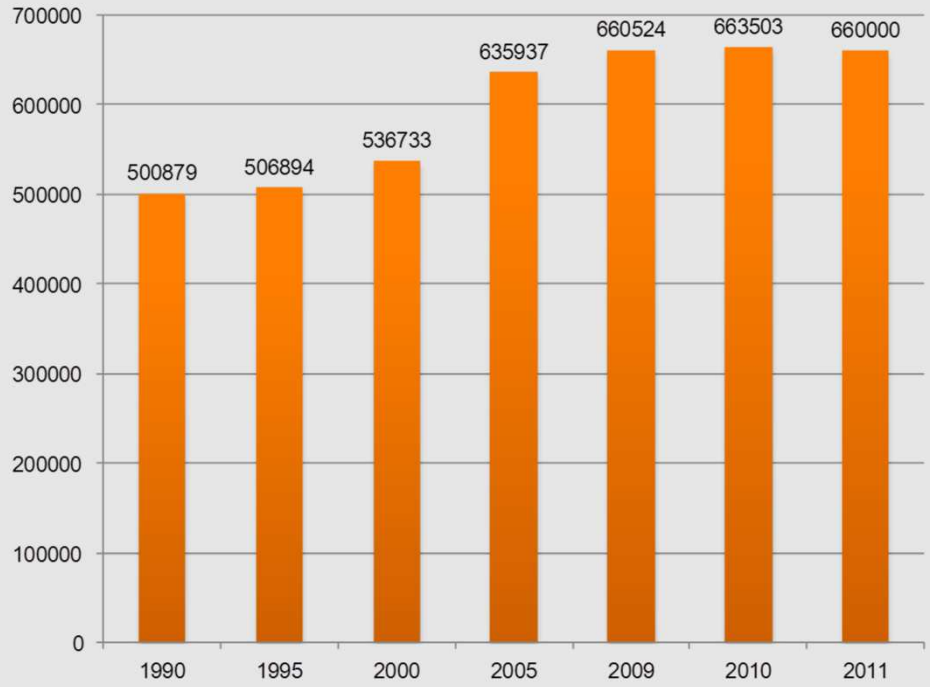
Clinical trials (n=174) in phase II & III

%-ages



Employees in the European Pharmaceutical Industry

- EFPIA Key Data 2012: EFPIA Companies alone directly employ 660,000 people in Europe,
- of this, 113,000 jobs are in R&D.



What is ‘Manufacturability’?

Definition

The ability to **manufacture** and **supply** a product **routinely** and **predictably** to the business requirements for quality, cost and scale in compliance with the appropriate Regulatory Authority and Health and Safety regulations

- (For Pharma) - Patients should always expect medicines to be available when needed and of the highest quality, safety and efficacy
- Manufacturers should manage new knowledge well, *improve processes and methods continually*, introduce new and better technologies, and do their best to avoid manufacturing quality related problems
- Manufacturing innovation across the industry has been stifled, which has resulted in ageing facilities replete with outdated process controls and equipment. In many instances of drug shortages, these conditions are the direct cause

Design for Manufacturability

Design for manufacturability is the general engineering art of designing products in such a way that they are easy to manufacture. The concept exists in almost all engineering disciplines, but the implementation differs widely depending on the manufacturing technology.

- Describes the process of designing or engineering a product in order to facilitate the manufacturing process in order to reduce its manufacturing costs
- Will allow potential problems to be fixed in the design phase which is the least expensive place to address them
- Other factors may affect the manufacturability such as the type of raw material, the form of the raw material, dimensional tolerances, and secondary processing such as finishing
- Addresses inconsistencies that arise during operation
- Applied in many areas but not particularly in chemical (pharma) manufacturing
- Consider what control strategy would be appropriate

https://en.wikipedia.org/wiki/Design_for_manufacturability

Pharma Manufacturing

Facts about API production

- The volume of active substance produced for commercial use ranges from a few kg (high potency, rare diseases) to several 100 tonnes (antibiotics, NSAIDs)
  - During R&D the requirement is normally 10-100 kgs (pilot plant)
- In general, production is conducted in batch mode on 4-6000 L scale at most
  - Operating in a continuous mode (e.g. flow chemistry) is gaining momentum
- Strict GMP (Good Manufacturing Practices) regulations apply
- The previous paradigm where most of the active drug was made in-house has now changed in favour of extensive outsourcing

Producing APIs – Desired Process Attributes

- Short
- Convergent
- Catalytic (key component of Green Chemistry concept)
- Atom efficient
- Amenable to telescoping (in situ/one pot operation)
- Minimum number of solvent swaps
- Operable in water/tolerant to water
- Simple purification – preferably by extraction and/or crystallization
- Environmentally concerned
- Scalable
- Robust in performance (offering predictable yield and quality)
- Intrinsically safe
- Freedom to operate
- Cost conscious

En route to sustainable manufacturing

Going Green: Prioritized Engineering Areas

Key research areas from a pharmaceutical and fine chemicals industry perspective

Rank	Main Key Areas	Sub-Areas/Aspects	Vote
1	Continuous Processing	Primary, Secondary, Semi-Continuous	12
2	Bioprocesses	Biotechnology, Fermentation, Biocatalysis, GMOs	11
3	Separation and Reaction Technologies	Membranes, Crystallizations	11
4	Solvent Selection, Recycle and Optimization	Property Modeling, Volume Optimization, Recycling Technologies, In-Process Recycling, Regulatory Aspects	10
5	Process Intensification	Technology, Process, Hybrid Systems	9

The Concept of Green Chemistry

IUPAC definition

”The invention, design, and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances”

The 12 Principles of Green Chemistry

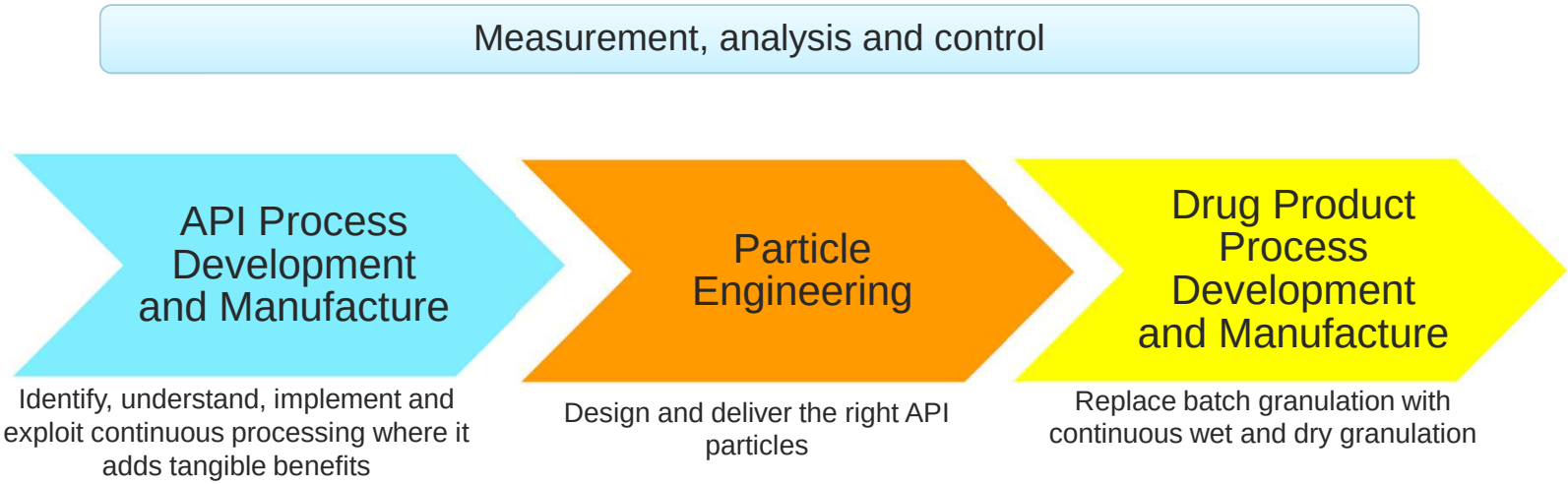
1) Minimise waste
2) Maximise reaction efficiency
3) Less hazardous synthesis
4) Safer reagents
5) Safer solvents
6) Energy efficiency
7) Renewable feed-stocks
8) Reduce derivatives
9) Use catalysis
10) Biodegradation
11) Real time analysis
12) Accident prevention

Anastas, P.T.; Warner, J.C. Green Chemistry: Theory and Practice; Oxford University Press, 1998
Anastas, P.T.; Kirchhoff, M.M. *Acc. Chem. Res*. **2002**, *35*(9), 686-694
Scalable Green Chemistry. Case Studies from the Pharmaceutical Industry; Koenig, S. G., Ed.; Pan Stanford Publishing, Singapore, 2013

A Strong and Diverse Technology Platform

- Advanced synthetic chemistry
  - Asymmetric transformations
    - Screening for best catalyst/ligand
    - Catalytic predictions
    - Biocatalysis is making strong inroads
  - Cross-coupling reactions
    - Suzuki, Heck, Buchwald-Hartwig etc
  - Construction of complex molecular frameworks
    - Making unconventional (complicated) heterocyclic motifs
- Process Intensification
  - Continuous processing built on flow chemistry
    - A new paradigm with huge potential, but clear limitations
    - In practical use, but the full scope still needs to be defined
- Reaching sustainability by means of adopting Green Chemistry Principles
  - A major trend in API manufacture
  - Smart solvent selection will underpin green ambitions
  - Vision: Good processes are, by default, green

Continuous Processing



Deliver API quickly, safely, economically, reliably and in an environmentally friendly way

Continuous Manufacturing – Drivers/Blockers

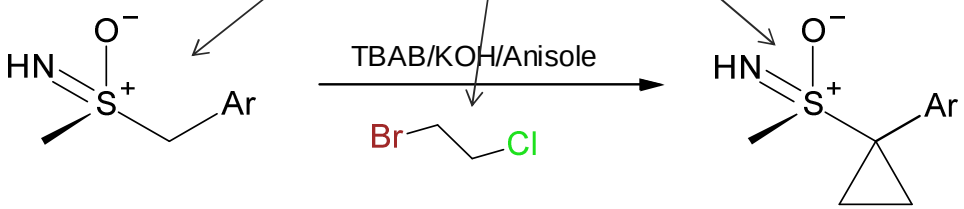
- Drivers
  - Speed – once flow parameters have been identified
  - Safety aspects when running hazardous chemistry
  - Feeling of urgency as ”everyone” does flow
  - The view is that continuous manufacture greatly reduces environmental footprint
  - Cost saving by virtue of better utilization of raw materials
- Blockers & Questionmarks
  - Width and breadth of reaction scope
    - Slurry reactions; precipitations
  - Limited attractiveness when only a small part of a process is operated in continuous mode
  - Small volumes vs. large volumes on commercial scale – unclear about financial benefits
  - Role of flow processes in the large molecule space (considering that many big pharma will aim for 30-50% biomolecules in their portfolios)
  - Regulatory concerns
  - Quality assurance – ensuring appropriate traceability
    - QbD (Quality by Design) might provide a solution

Two Phase PTC Cyclopropanation

Poor Stability

Two-phase system, difficult to mix

Degrade under batch reaction conditions



Non – robust process in batch 30-60% variable yield

Under flow conditions

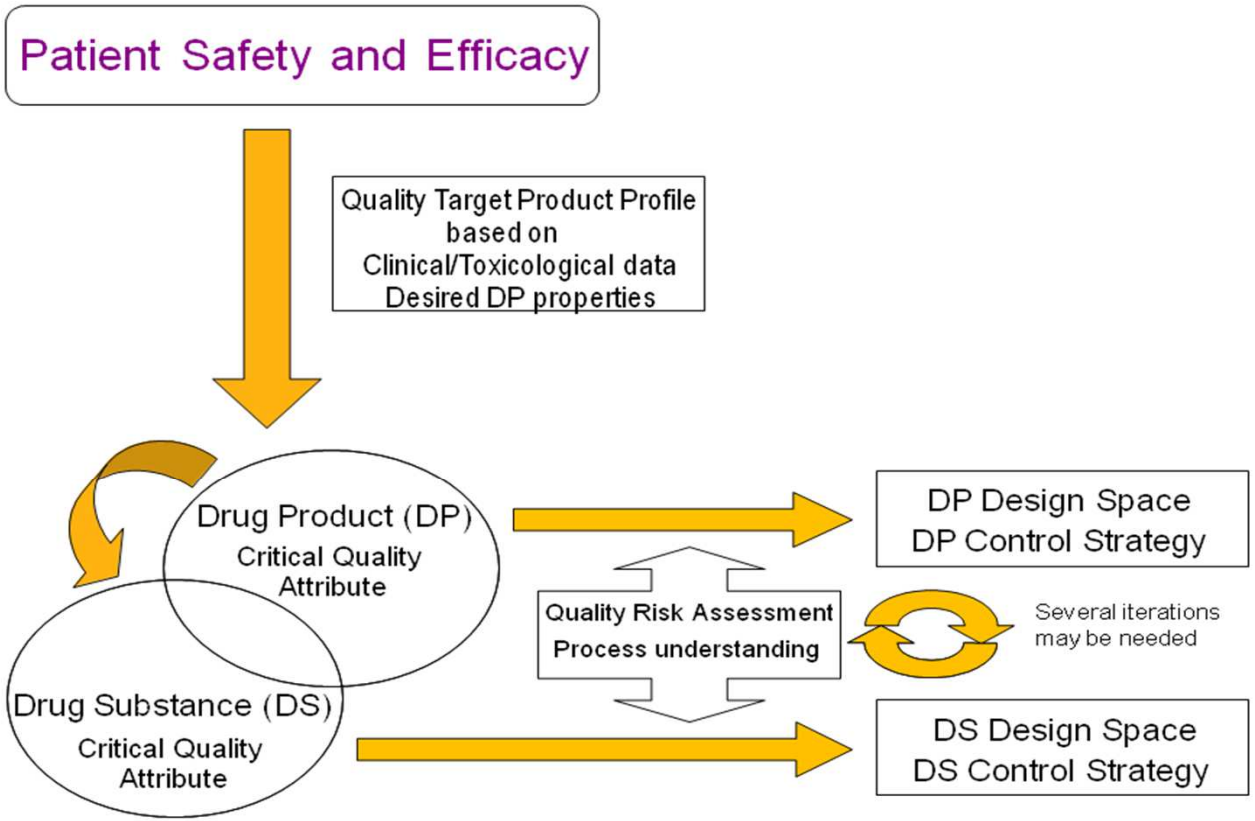
- Control – reaction temp= 60 °C
- Fast reaction – residence time= 4 min
- Improved mixing – 100 µm nozzle for anisole
  feed with a 2 bar pressure drop gives optimum emulsion
- Flexible manufacture
- Substrate protected
  - Any problems and pumps can be stopped

Two successful Large Scale Laboratory manufactures (0.6 & 4 kg)
at 74% yield, now ready to outsource!

O'Kearney-McMullan, A. (AstraZeneca); unpublished results

The Quality by Design Framework

The concept of QbD for Drug Substance and Drug Product



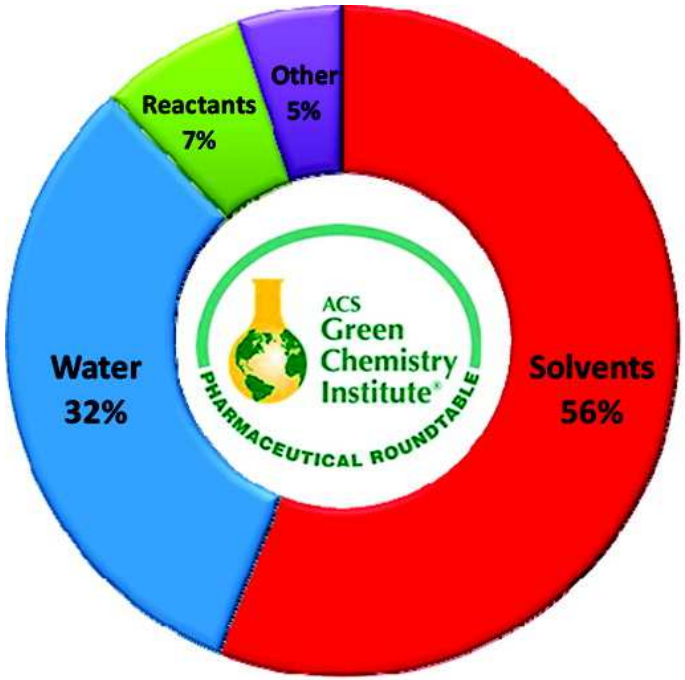
Courtesy Maria Edebrink & Talia Buggins, AZ Sweden/UK

Pharma and sustainability

- Pharma spends a lot of time stirring adulterated solvent

Time = costs
Quantities = waste

- Corporate sustainability targets
  - *Senior management/board interest*
  - *'Good news' message*
- Regulatory environment
  - *REACH...*



Process Mass Intensity Benchmark

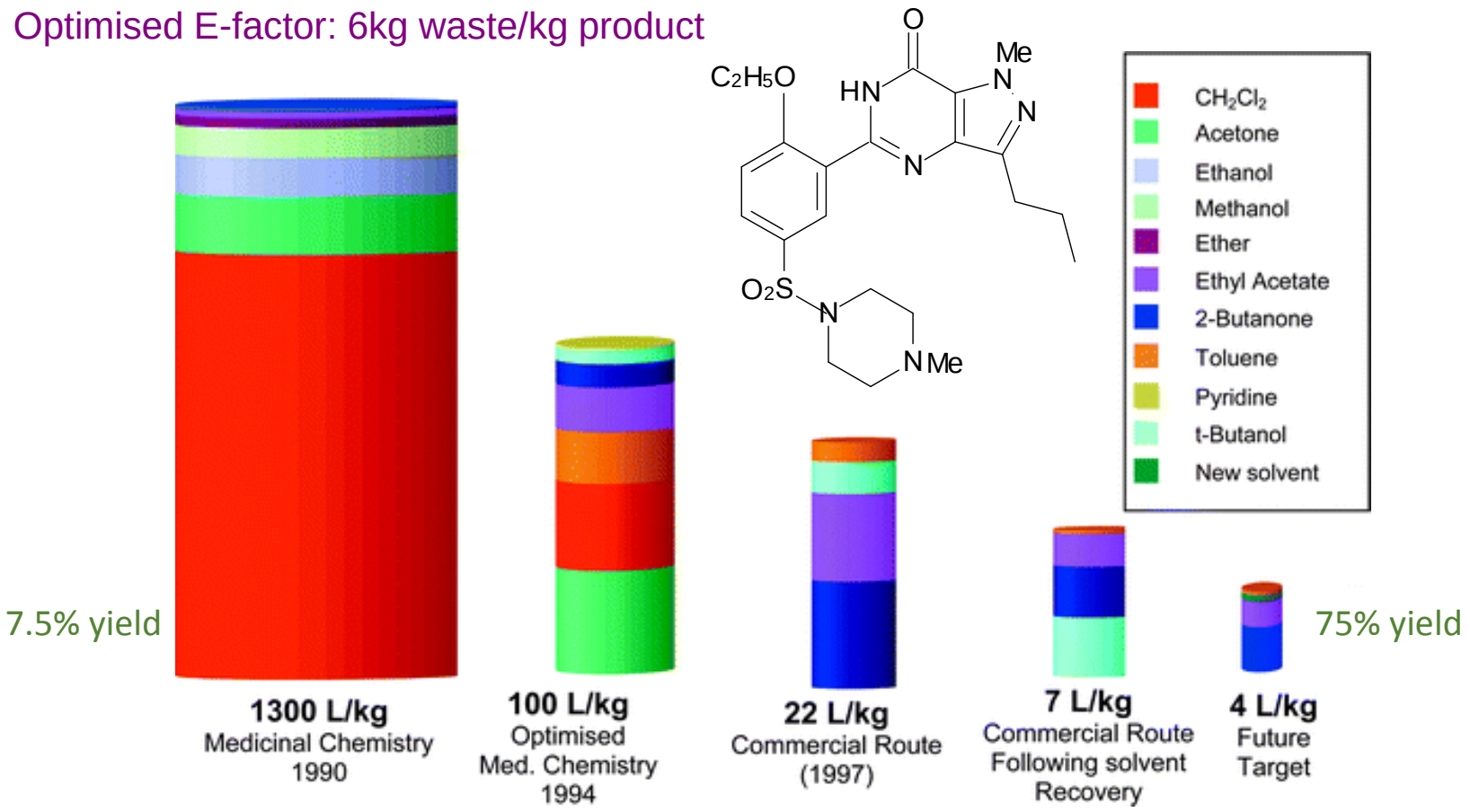
Addressing this is the ethical thing to do
Scientifically highly challenging

Jimenez-Gonzalez, C; Ponder, C.S.; Broxterman, Q.B.; Manley, J.B. *Org. Process Res. Dev.* **2011,** *15*(4), 912-917
Federsel, H.-J. *Green Chem*. **2013**, *15*(11), 3105-3115

Efficiency in Solvent Utilization

Award Winning Green Chemistry to Pfizer (2003)
- The Sildenafil/Viagra® Case -

Optimised E-factor: 6kg waste/kg product



Dunn, P.J. et al. *Org. Process Res. Dev*. **2000**, *4*(1), 17-22; *Green Chem*. **2004**, *6*(1), 43-48

Driving Key Technology Concepts Forward

- Green chemistry and sustainability in all forms and shapes
  - Importance of solvent selection [Diorazio, L.J.; Hose, D.R.J.; Adlington, N.K. *Org. Process Res. Dev*. **2016**, *20*(4), 760-773]
  - Efforts to move away from transition/precious metals to base/non-precious metals (Izatt, B. M. et al *Chem. Soc. Rev*. **2014**, *43(8)*, 2451-2475)
  - Strong emphasis to move from batch to continuous manufacturing
    - ✓ Including down-stream processing
- Process intensification – Underpinning drivers
  - Higher production capacity per unit voulme
  - Better quality control for product properties
  - Objectives
    - ✓ Efficiency
    - ✓ Compactness
    - ✓ Economy
    - ✓ Safety
    - ✓ Green production
    - ✓ Cleanliness
- CH-activation as the main route to conduct substitutions?
- Microwave heating – a feasible principle on large scale? [Ritter, S. K. *Chem. Eng. News* **2014**, *92*(4), 26-28)]

Operating in a Data-Rich Environment

- The experimental set up of today offers access to vast amounts of data
- Analytical tools are available that allow the recording of a broad range of experimental results in real time
- The use of flow processes has made strong inroads
- Computers are well established in the experimental environment
- Self-optimization algorithms are available to help increasing the speed of exploration of complex parameter spaces[1,2]
- Huge demands on data storage and retrieval as part of a wider knowledge management system
- The visionary goal: Combining automated flow chemistry, real-time analytics, and algorithms might allow the synthesis of virtually any molecule in essence without human interaction[3,4]

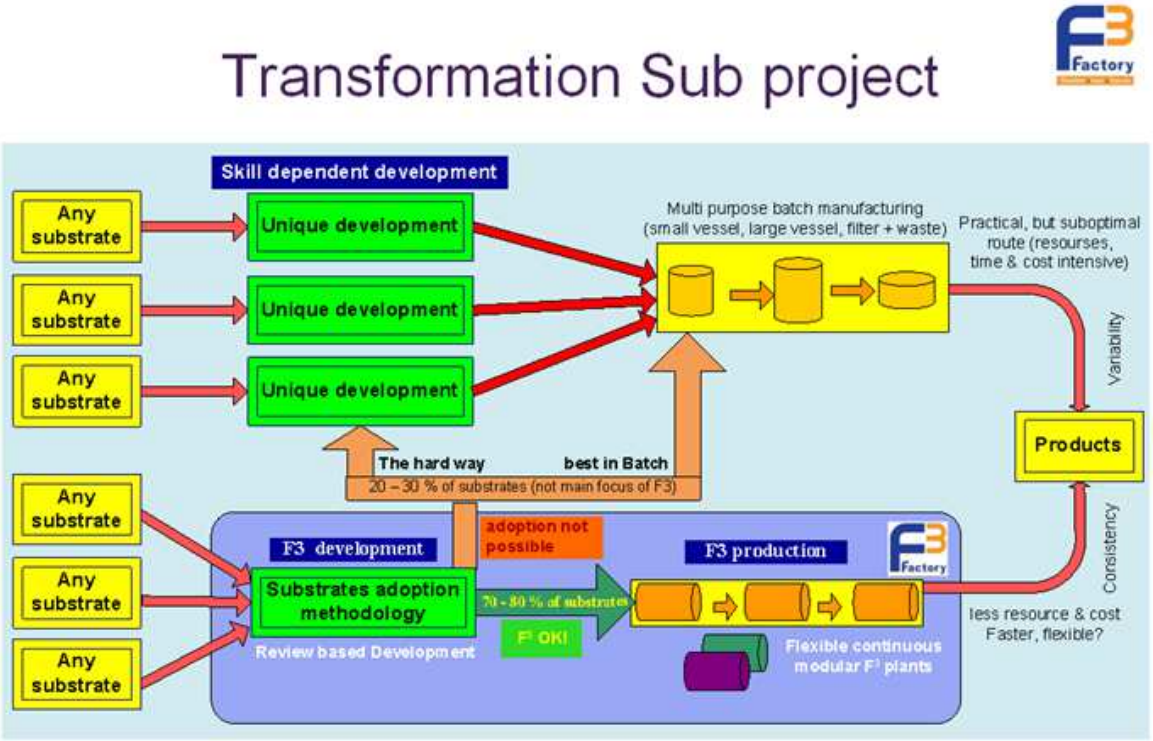
1. Parrott, A. J.; Bourne, R. A. et al *Angew. Chem. Int. Ed*. **2011**, *50*, 3788-3792
2. Holmes, N.; Akien, G. R.; et al *React. Chem. Eng*. **2016**, *1*, 96-100
3. Adamo, A. et al *Science* **2016**, *352*(6281), 61-67
4. Sans, V.; Cronin, L. *Chem. Soc. Rev*. **2016**, *45*(8), 2032-2043

From Vision to Reality: Fast Access to Complex Molecules

F^3 - EU financed project with > 20 partners and ca. €18 Mio budget

Purpose of the Transformation Sub Project :

- To develop and validate a generic methodology for the formation of pharmaceutical intermediates
  - Reducing cost of process development
  - Increasing throughput and improving robustness
  - Increasing manufacturing flexibility

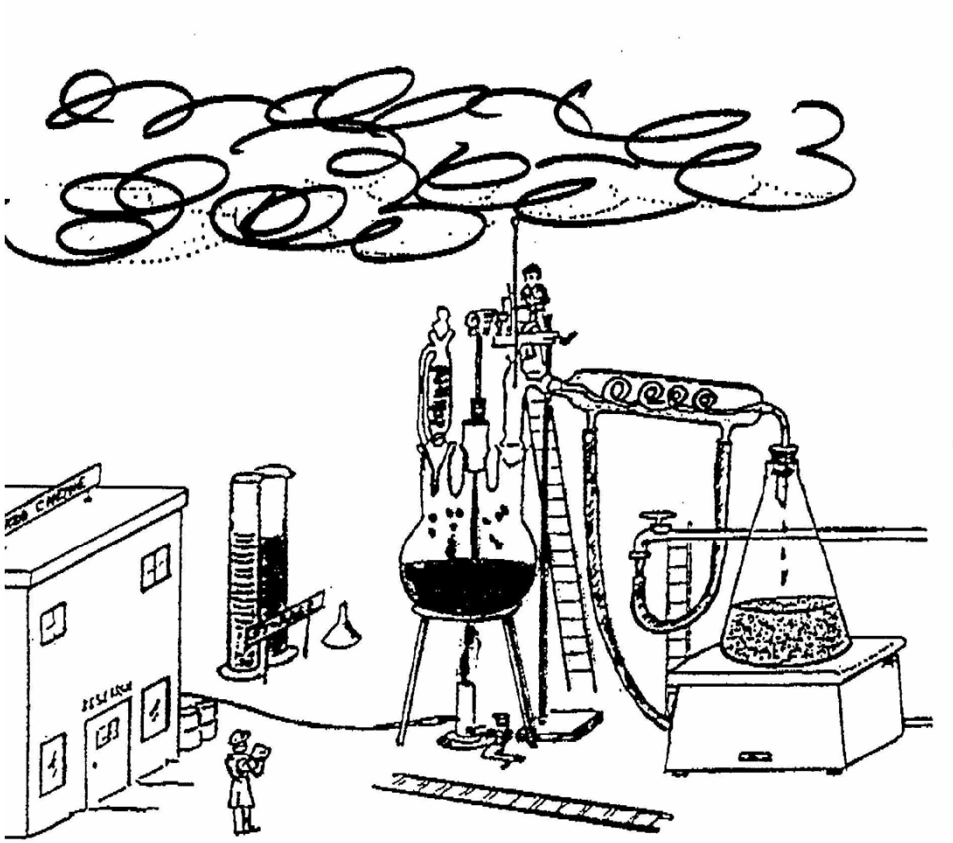


Conclusions & Outlook

- Manufacturability has emerged as a powerful concept in Pharma underpinning full scale manufacturing processes
- Reap the fruits from access to big data
- Continuous manufacture has become a mainstay in the pharma industry
  - Several successful applications have been demonstrated
  - Many pharma companies will ensure access to internal flow capabilities
- Be aware of limitations in the flow chemistry space
  - With the current technology many chemical transformations will not be accessible
- Biocatalysis is making strong inroads as a reliable and versatile technology
  - Immobilized enzymes offer excellent entry into processing under a flow regime
- The QbD framework enjoys broad appreciation in process design
- The F^3 concept provides a modularized production platform in a flexible container environment
- Futuristic capability: On-demand continuous flow production of pharmaceuticals

Thank you for your attention

Time for Q/A



The lab results were so good we bypassed process development