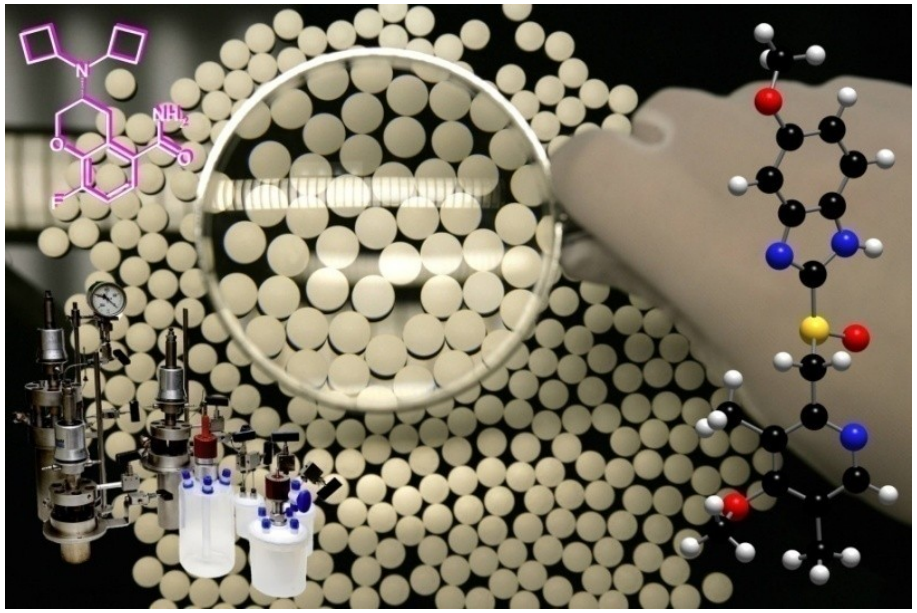
Molecules Improving Our Health

- The Impact of Chemistry on the Fight Against Disease -



Hans-Jürgen Federsel, Senior Principal Scientist

Pharmaceutical Development, AstraZeneca, Macclesfield, UK

hans-jurgen.federsel@astrazeneca.com

Lectures at the Universities of Bucharest and Cluj

Romania, October/November 2013

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RESEARCH & DEVELOPMENT
PHARMACEUTICAL DEVELOPMENT

Contents of the Lecture

- Introduction about my
  - Company
  - Department
- The pharmaceutical landscape – The big picture
  - The situation today
  - Major challenges
- The discovery process
- Taking laboratory chemistry to manufacturing scale
- The era of green chemistry
- Route design – The hunt for the best
- Hot spots in process chemistry
- Summary & Outlook

Short Introduction

My Company and my Department

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AstraZeneca & Pharmaceutical Development

- Created in a merger between Astra (Swedish) and Zeneca (British) in 1999
- 57.200 employees worldwide (going down towards 50.000)
  - 10.000 in R&D (≈17% of all staff) – to be reduced to 7.700 by 2016
  - Research sites: Mölndal (close to Gothenburg, Sweden), Alderley Park and Macclesfield (close to Manchester, UK), Gaithersburg, MD (US), Bangalore (India), Shanghai (China)
- Financial data (2012)
  - Sales: $27.9Bn
  - Profit: $10.4Bn
  - Investment in R&D: >$4Bn (≈14% of sales)
- Products available in >100 countries; major brands
  - Crestor® (cholesterol-lowering), Seroquel® (mania, depression), Nexium® (anti-ulcer), Symbicort® (respiratory), Arimidex® (cancer), Brilinta® (antiplatelet)
  - Late stage portfolio comprised of i.a. selumetinib (non small-cell lung cancer), olaparib (solid tumours, e.g. ovarian), diabetes franchise
- Pharmaceutical Development has ≈ 1000 people
  - Chemical Development: Process chemistry, analytics, engineering
  - Product Development: Formulation, packaging
  - Others: Supply Chain, Projects Management, Quality Assurance

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The Bigger Picture

The World of Pharma

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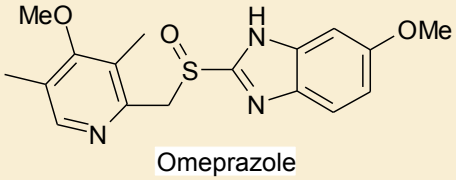
What is a drug?

Active substance



Omeprazole

Formulation

Package

Information

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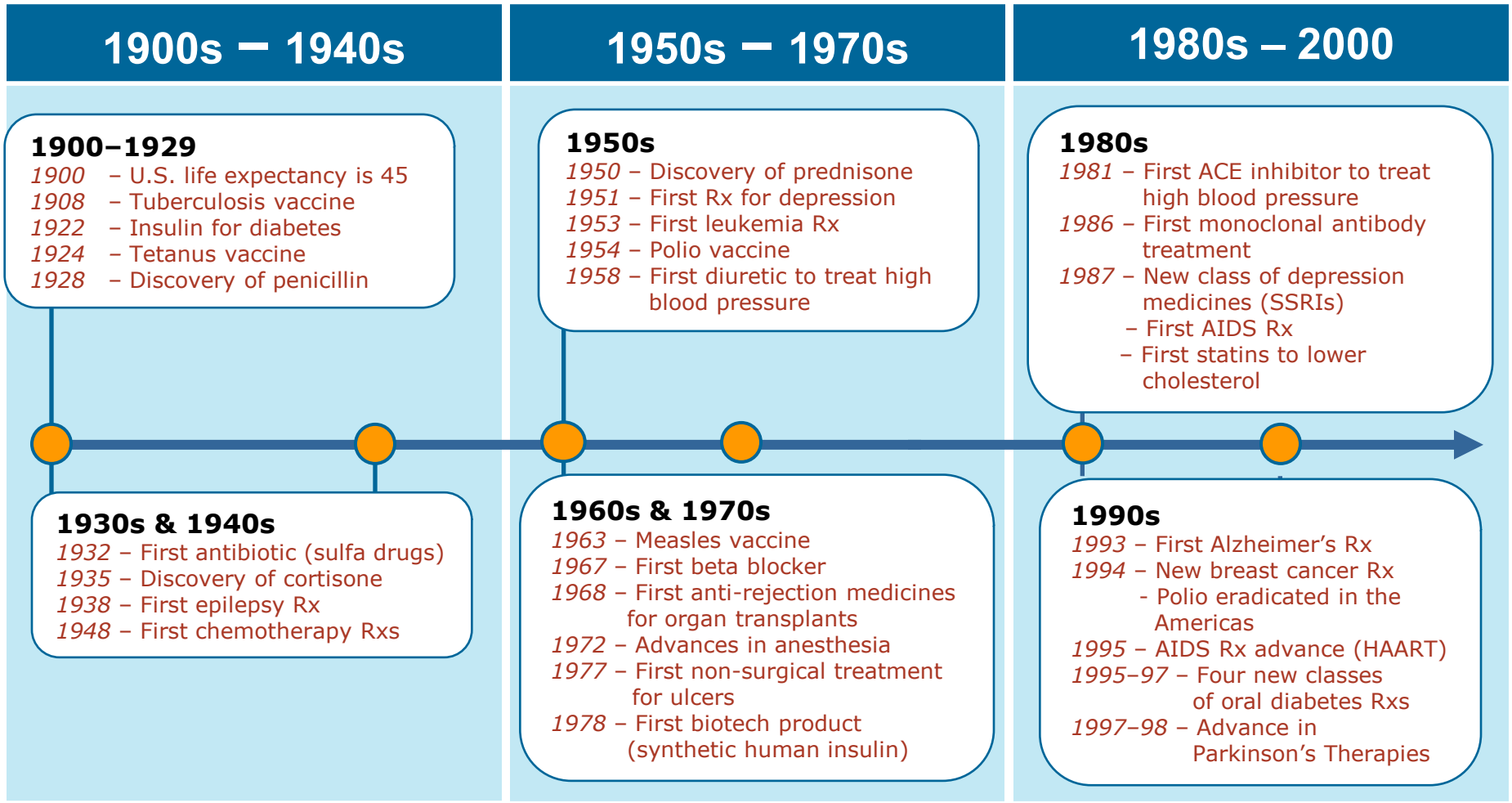
Selected Advances in the 20th Century



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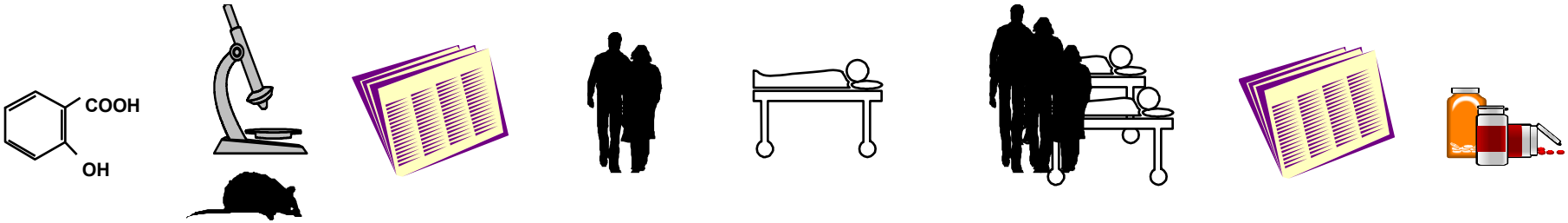
The Pharmaceutical Industry Landscape

- Historically, a very successful franchise
  - Today a mix of small and large (biopharmaceutical) molecules
- The megabrand strategy (annual sales > $1Bn) has dominated for a long time
- Industry consolidation – mergers, acquisitions (pharma/pharma, pharma/biotech)
- A productivity crisis – Too few new drugs reach the market
- Escalating costs
- Complex (often poorly understood) diseases being addressed
- Tough regulatory demands, especially on safety and efficacy
- IP (Intellectual Properties) and patent rights under constant attack from competitors and generics
- Price pressure from health authorities, patients, payers, media
- More money invested in R&D than ever before (>$70Bn by Global Pharma)
- Unprecedented availability to broad range of technologies
- Access to global talent pool
- Intense collaboration with external partners

Major Challenges

- Low productivity expressed as launches of novel medicines per year
- Timelines from idea to market too long (often >10 years)
- Extremely costly business with no or at best low predictibility of success
  - Overall success rate is 6-7% (constant decline since 1995)
- Addressing diseases with unmet medical needs, often lacking detailed (validated) mechanistic understanding, for example
  - Stroke
  - Dementia (e.g. Alzheimer)
  - Obesity
  - Diabetes II
  - Cancer
- Patent expirations
  - Projection: During the period 2006-2015 products summing up to a value of $123Bn will loose patent protection globally

From idea to registered drug



Target--> Chemistry
Search for active substances

Pharmacology
Toxicology, efficacy-studies on various types of animals

Authorities
Application for permission to administer a new drug to humans

Phase I
Safety and tolerability studies on approx. 100 healthy persons

Phase II
Safety and efficacy-studies on a limited scale, approximately 200 patients

Phase III
Comparative studies on a large number of patients.
1000 - 5000 patients

Authority
Application for permission to market a new drug

Phase IV
Continue comparative studies

Level of knowledge

Pre-Clinical studies ----------> *Clinical studies*

1	2	3	4	5	6	7	8	9	10

Timeline (years)

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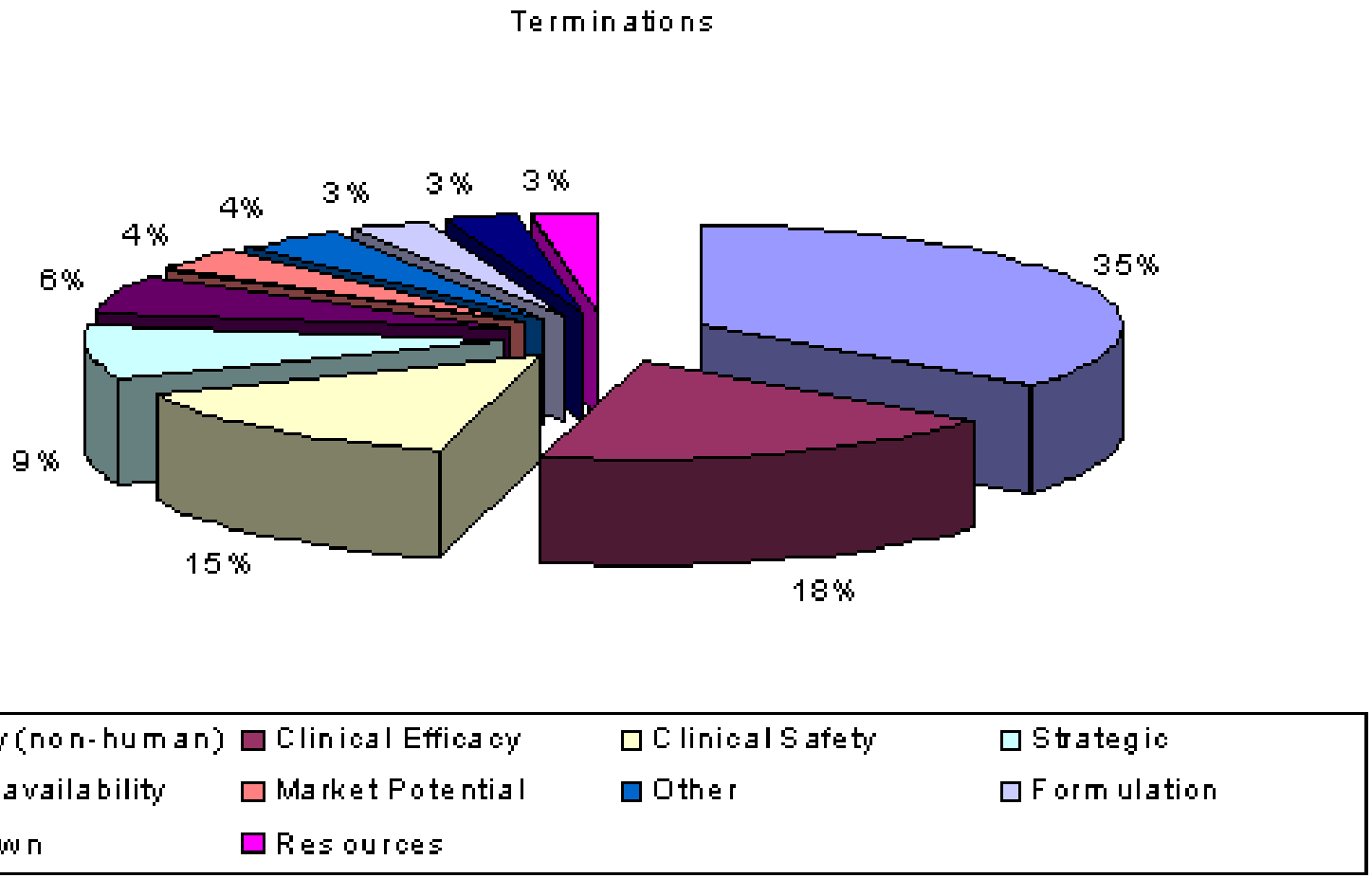
Causes for Failures



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Steps on the Way to a Novel Medicine

Steps to be Taken During the R&D Phase

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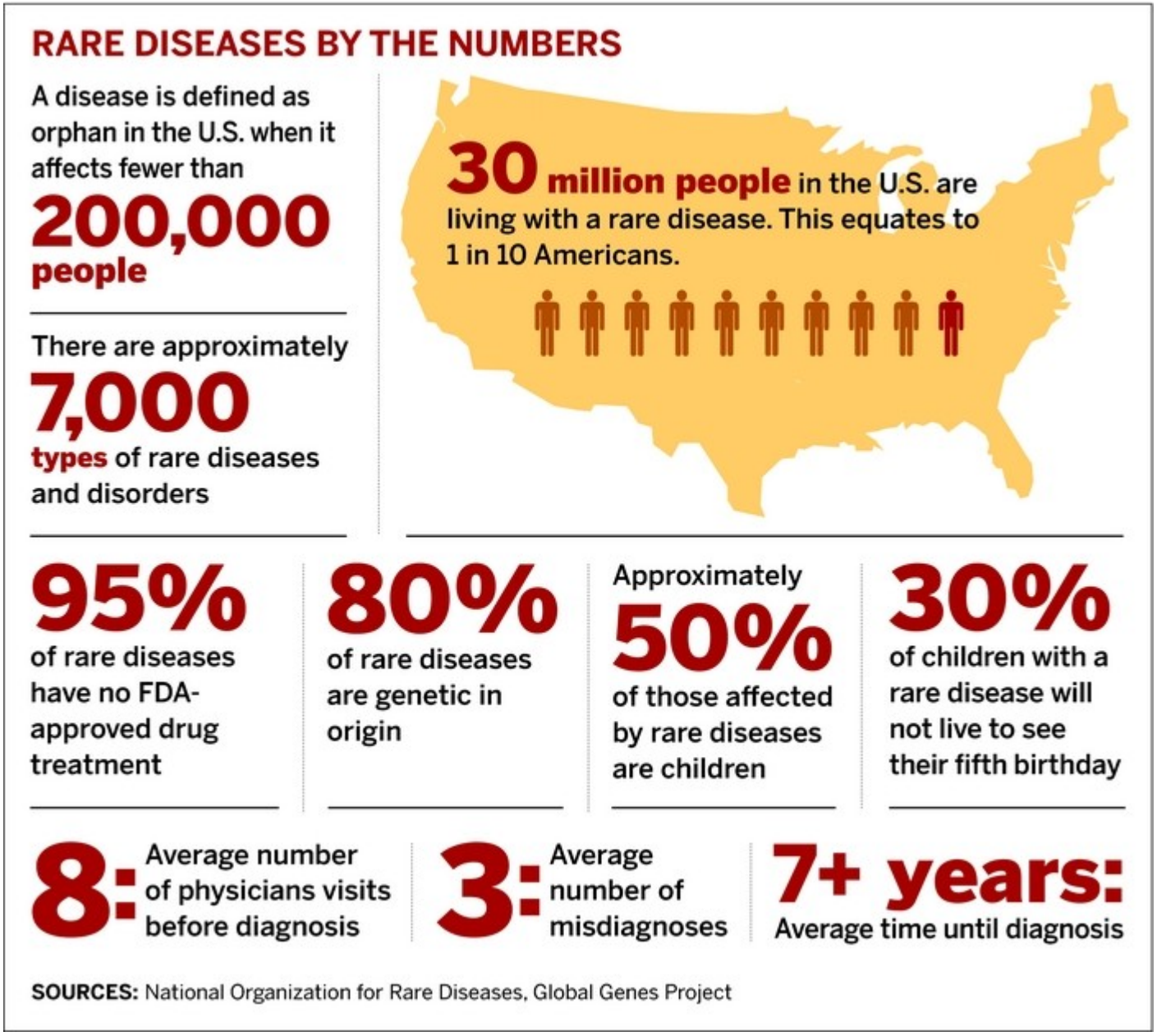
Developing a New medicine is….

- Multidisciplinary – Biology, Chemistry, Toxicology, Pharmacology, Pharmaceutics, Medical Science etc
- Lengthy (8-10 years or longer)
- Costly (>$1Bn)
- Risky – less than 1 pre-clinical drug project out of 10 makes it to registration
- Complex
- Challenging
- Innovative
- Competitive
- Profitable (if you are lucky)
- Needed – Many diseases with a poor treatment paradigm or none at all (e.g. the plethora of orphan diseases)

Medical Challenges for the Future



Jarvis, L.M., *Chem. Eng. News* **2013**, *91* (19), 10-12

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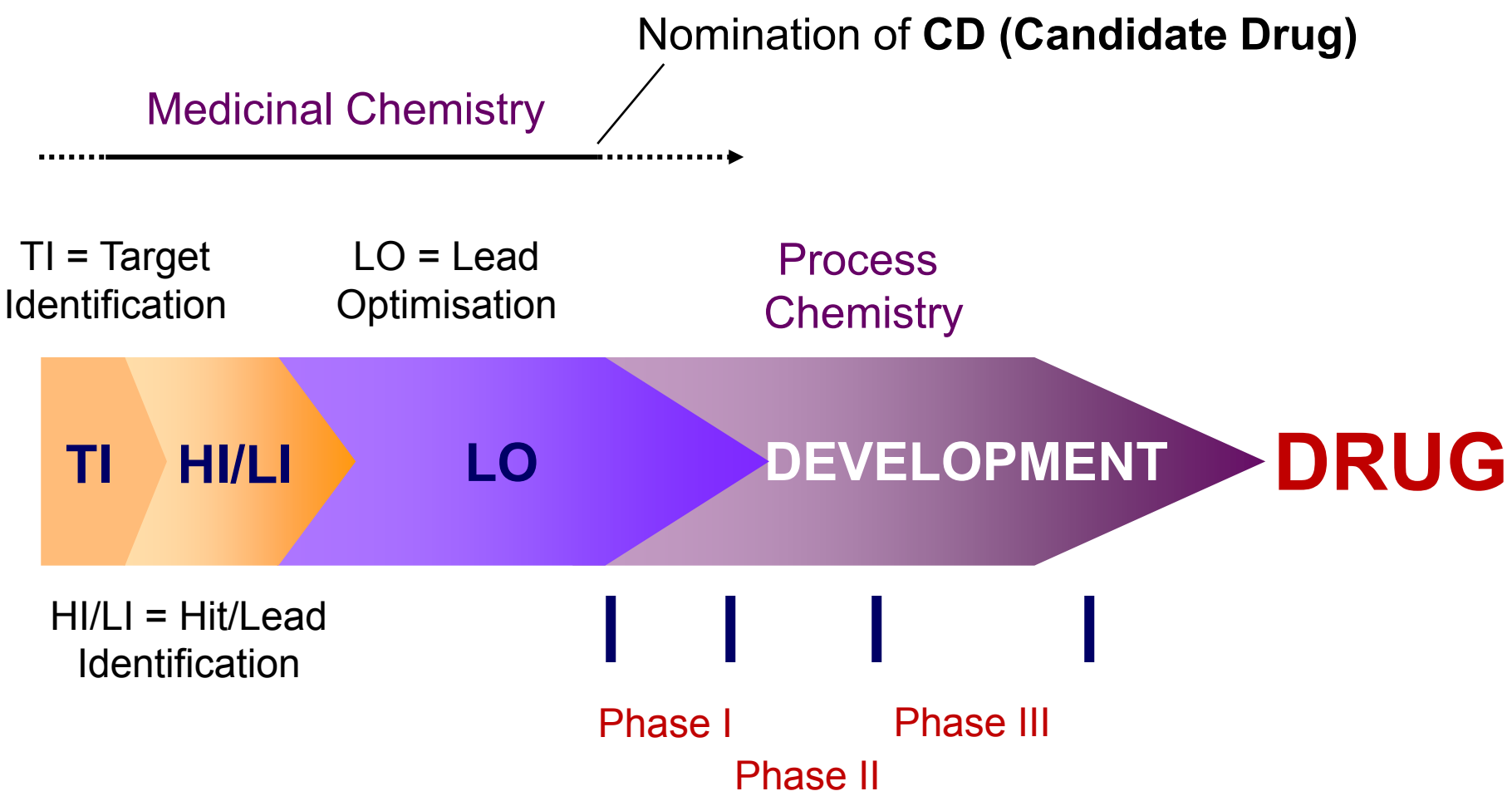
The Role of Chemistry



Synthetic chemists involved from early discovery phase to launch

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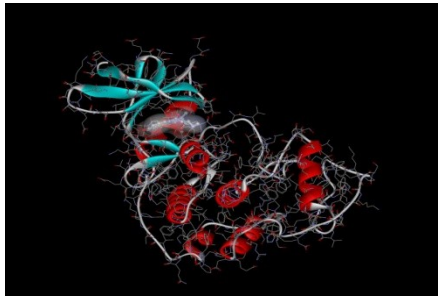
The Steps from Biology → Chemistry

Disease → Biological mechanism -> Target → Develop assays

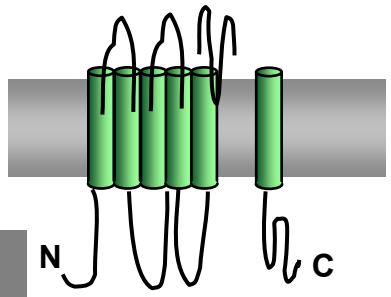
Chemical starting points:

3D Structure?
Similar proteins?

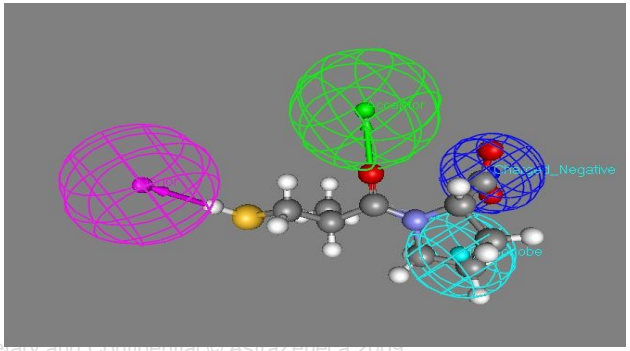


Screen the compound library

Directed screening (e.g., ion channel active compounds)



Known active compounds?
Natural (endogenic)?
Non-natural (synthetic)?



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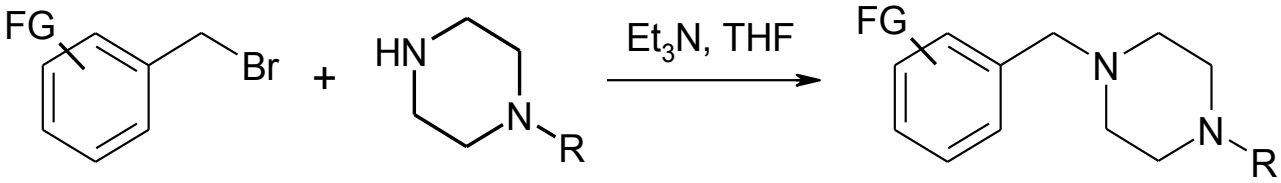
The Biological Targets

Where current drug molecules exert their effect

- G-Protein Coupled Receptors (GPCRs) – [awarded the 2012 Nobel Prize in Chemistry!]
- Enzymes
- Hormones
- Ion Channels
- Nuclear Receptors
- DNA
- Other target-rich protein families: Proteases, kinases, phosphatases

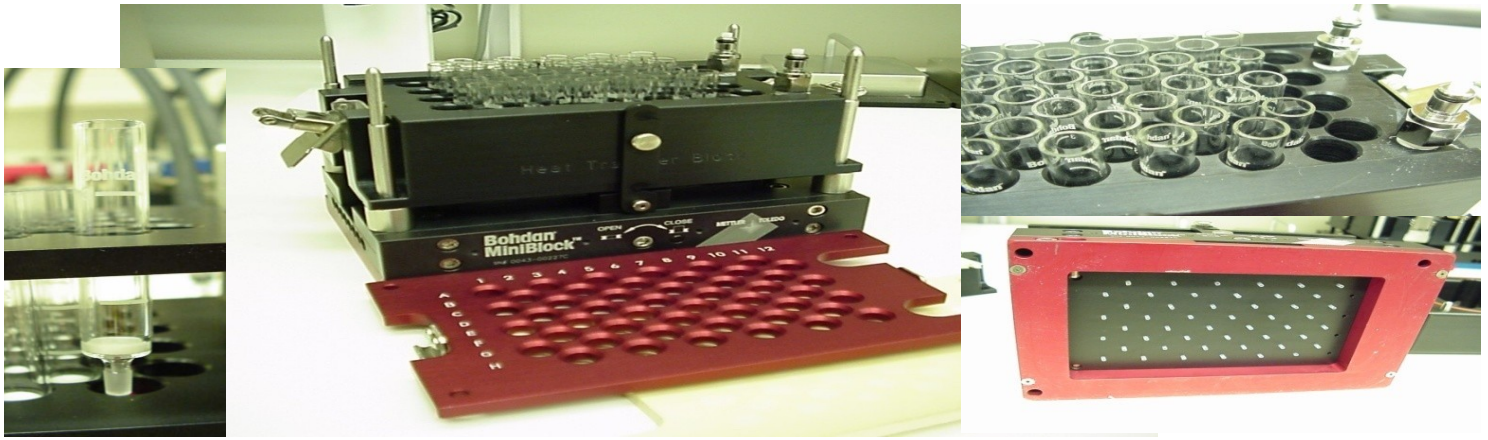
Parallel Synthesis



Reactant 1:
6 different

Reactant 2:
8 different

48 different product molecules



Several reactions in parallel – useful for

- synthesis of several **different compounds** simultaneously
- screening of **different reaction conditions** for preparing one specific compound

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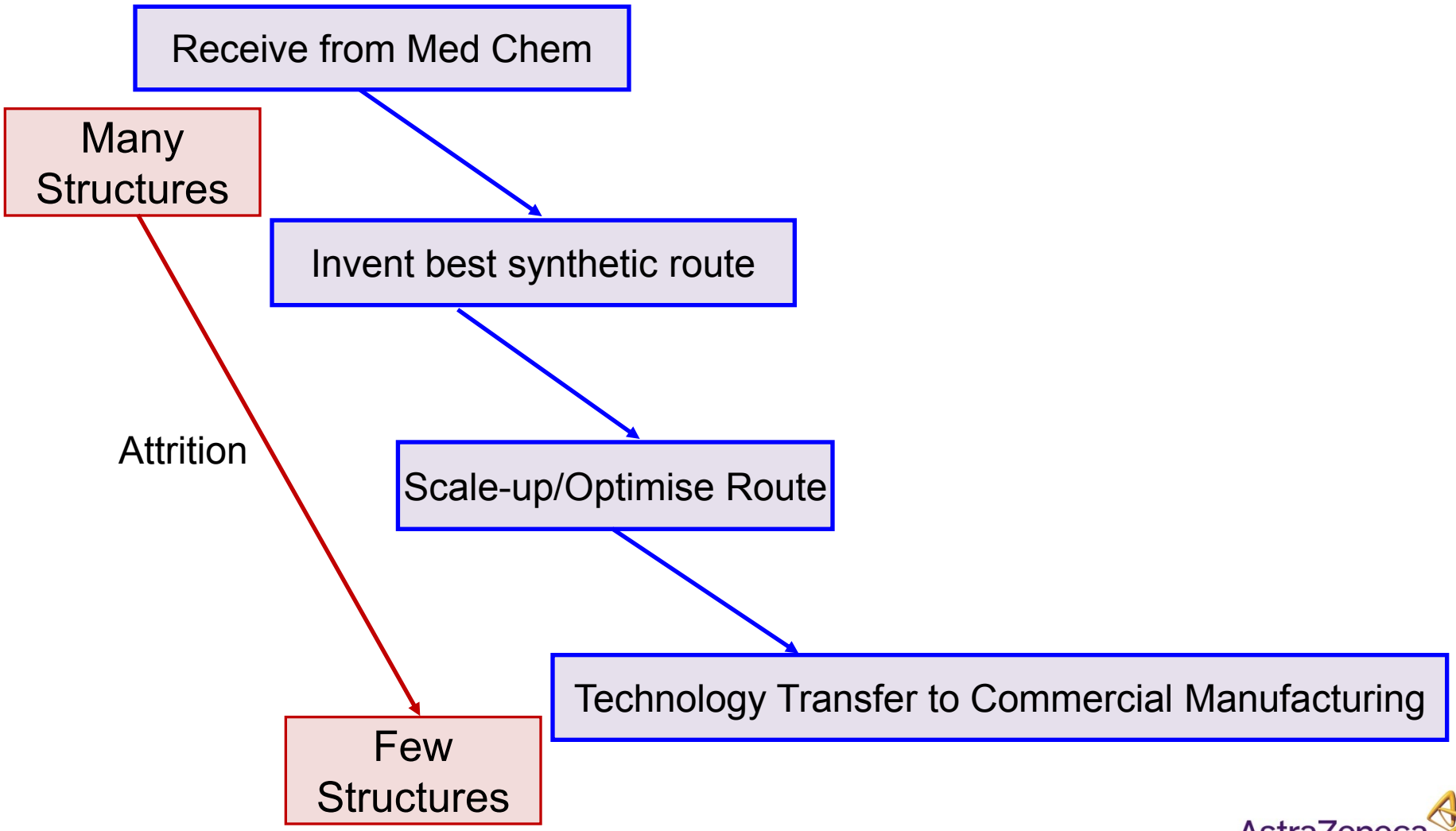
From Med Chem to Production



Federsel, H.-J. *Drug News Perspect*. **2008**, *21*(4), 193-199
Federsel, H.-J. *Acc. Chem. Res*. **2009**, *42*(5), 671-680

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Is Scale up Trivial?

It depends

- Experience from similar reactions and/or compounds
- How good does the final process have to be – small vs. large quantities
- Purity criteria
- Interfering patents
- The timelines for the project

What is different to running in the laboratory

- The amount of chemicals/solvents used give higher risks and hazardous scenarios to take into account
- Large scale equipment has an intrinsic inertia meaning that heating/ cooling takes considerably longer time
- Technical discrepancies, e.g stirring is less efficient, addition of reagents takes longer, separation times are extended
- Cross-contamination from other production campaigns due to inefficient cleaning procedures poses a risk of compromising product quality

Characteristics of Highly Efficient Syntheses

- 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

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) regulation applies
- The previous paradigm where most of the active drug was made in-house has now changed in favour of extensive outsourcing

Small vs. Large – Controlling Exothermic Reactions

A common procedure at small scale in a research lab

- Charge solvent and all reactants at low temperature, then heat the reaction mixture

$\Rightarrow$ Might lead to a runaway reaction!

Safer alternatives at larger scale

- Add one reactant slowly, at a temperature which gives fast conversion ($\Rightarrow$ no heat accumulation)
- Use a continuous flow reactor

Combining Molecules & Processes

Introduction

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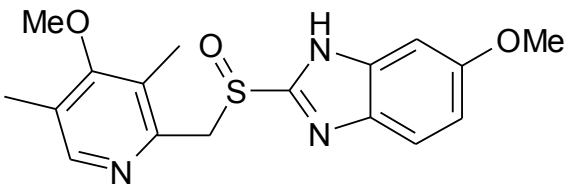
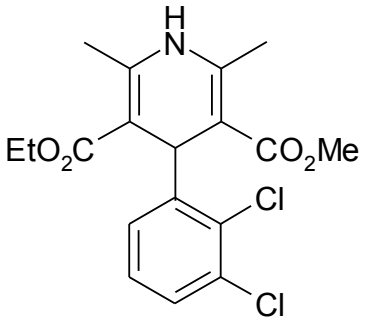
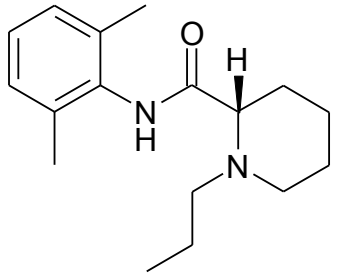
Molecules that Made It– Success Stories



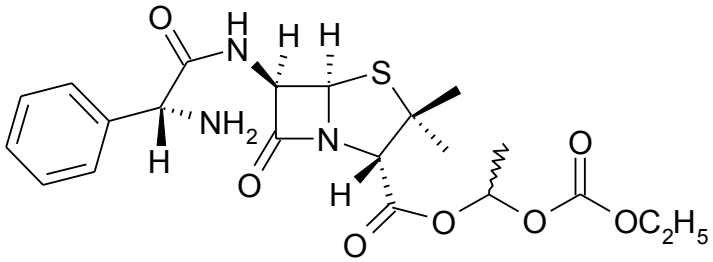
Omeprazole



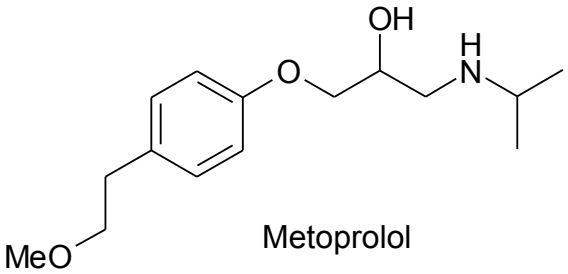
Felodipine



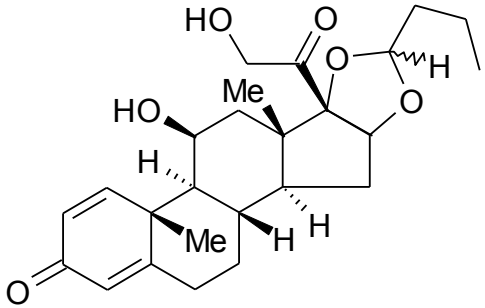
Ropivacaine



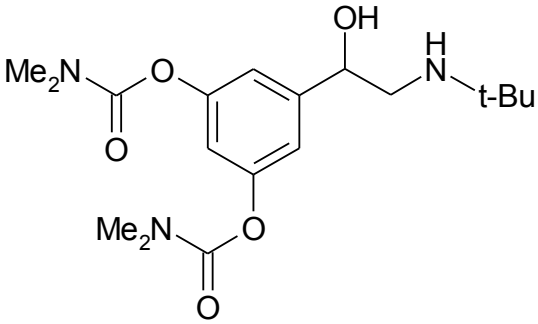
Bacampicillin



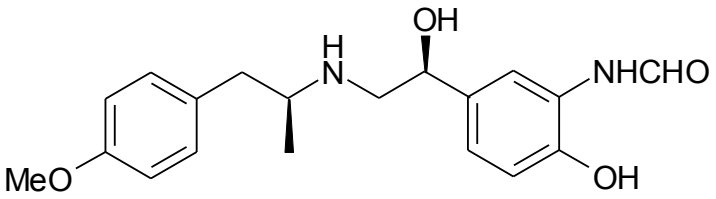
Metoprolol



Budesonide



Bambuterol



Formoterol

Structures of APIs (Active Pharmaceutical Ingredients)

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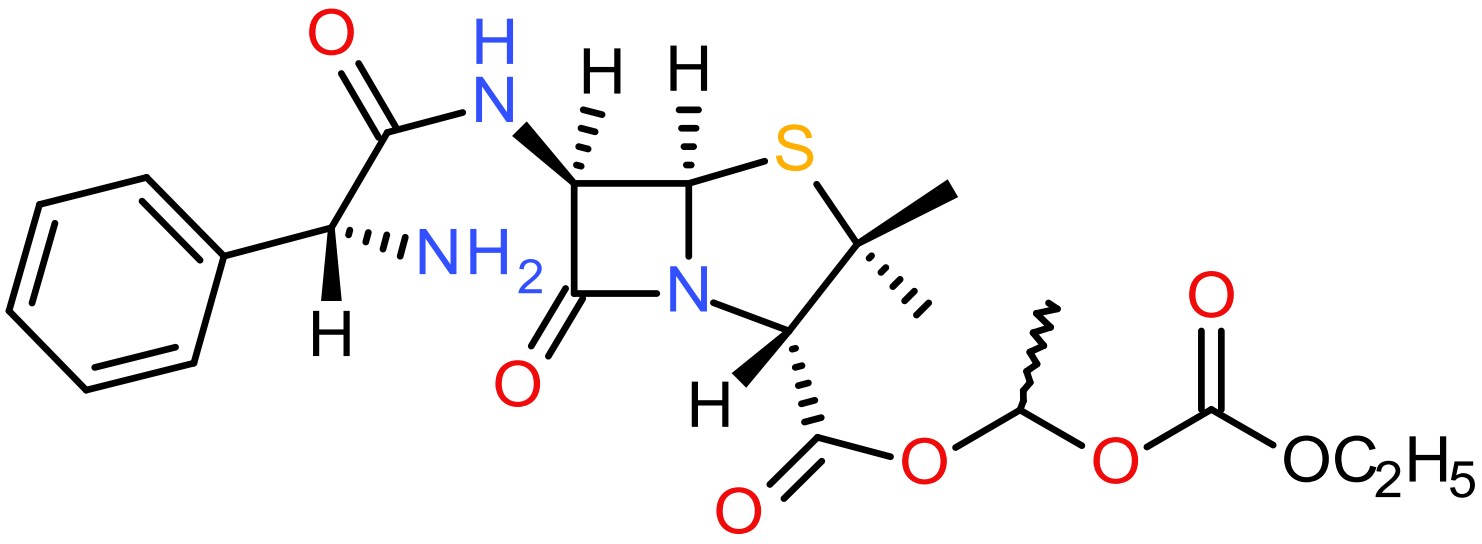
Optimizing a Commercial Penicillin Process



Bacampicillin (Penglobe®)

- A semi-synthetic pro-drug with high oral bioavailability
- Launched in the mid 1970s
- Annual production volume > 100 tonnes

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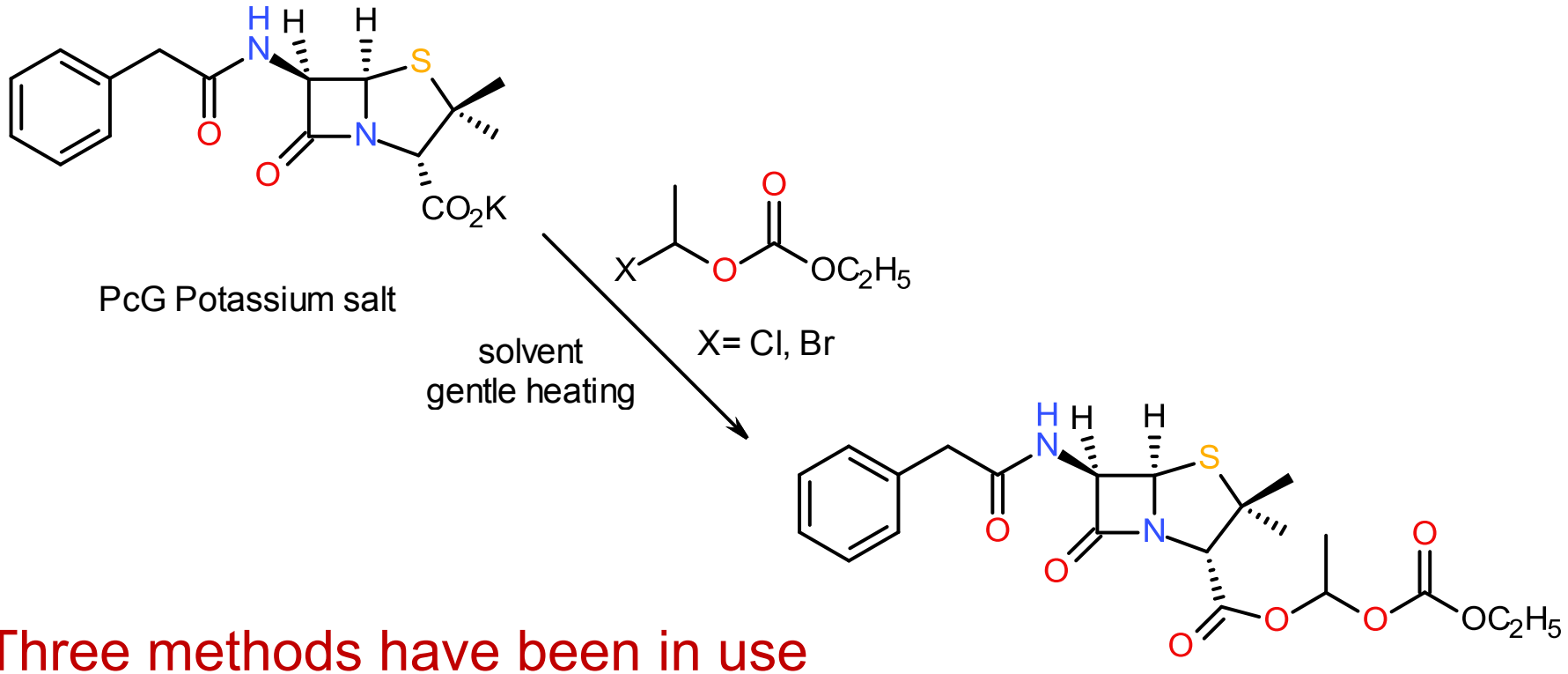
ß-Lactam Antibiotics

- Foundations of bacteriology established during 19th century
  - Pasteur & Joubert (1877); Inhibition of *Staphylococcus* (Garré)
  - Bacterial product (*Pseudomonas aeruginosa*) in clinical practice for treatment of diphteria (1890)
- Landmark discovery by Fleming in 1928-29 (Oxford, UK) of antibacterial activity exerted by *Penicillium notatum*
  - Systematic studies of antibacterial substances in the 1930s
    - Isolation of a penicillin salt, albeit in an impure form (Florey, Chain)
  - First patient treated with a penicillin in Feb 1941
- Identification of other microbial compounds (gramicidin, Dubos; streptomycin, Waksman [1943])
- Cephalosporins discovered in Italy by Brotzu (1945)
- 1945 Nobel Prize in Medicine to Fleming, Florey, Chain
  - Contacts with Chain gave Astra a flying start – first product in 1949

First Step in Process



Three methods have been in use

- X=Cl/acetone at ~ 50 °C/>15 h gave black solution with 90% product content
- X=Cl/DMSO at ~ 40 °C/8-9 h gave dark coloured solution with 97% product
- X=Br/acetone at ~ 40 °C/4½ h gave slightly yellowish solution with 99.5% product

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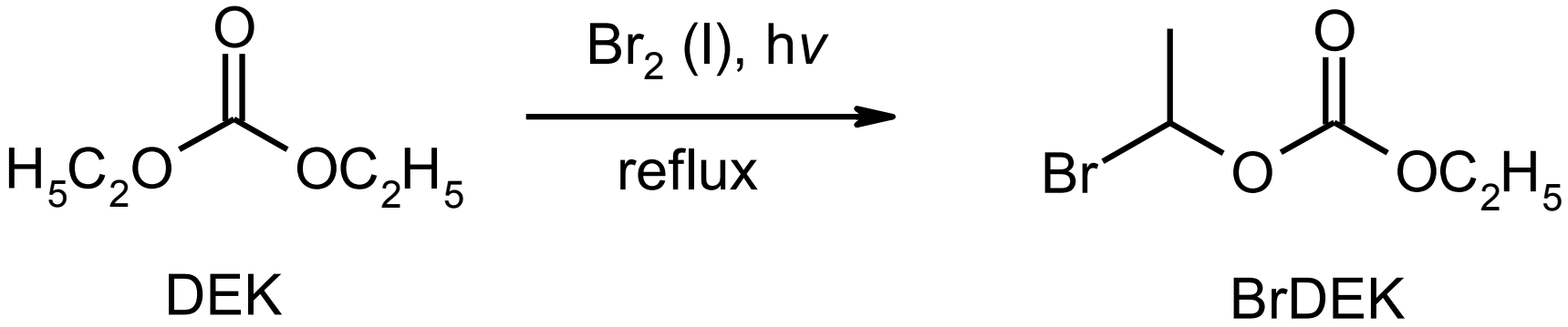
How to Manufacture BrDEK



DEK BrDEK

Highlights

- Photobromination only feasible route
- Overbromination is a serious problem requiring a flow process to be designed
- Main impurities formed are α,α'- and α,α-dibromo derivatives
- Investigations showed that running at ~35% bromination degree was optimal
- Running in refluxing DEK (~130 ^{o}C) ensured efficient removal of HBr
- Commercial production (> 100 tonnes/annum) in cascade mode using three glass reactors in series
- Semi-batch production mode

Together with André M. Braun, EPFL, Lausanne, Switzerland;
see Technologie Photochimique, Presses polytechniques romandes, 1986; p.324
Brit. Pat. 822,622 (1982)

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Shades of Green

The Drive Towards Sustainability

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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

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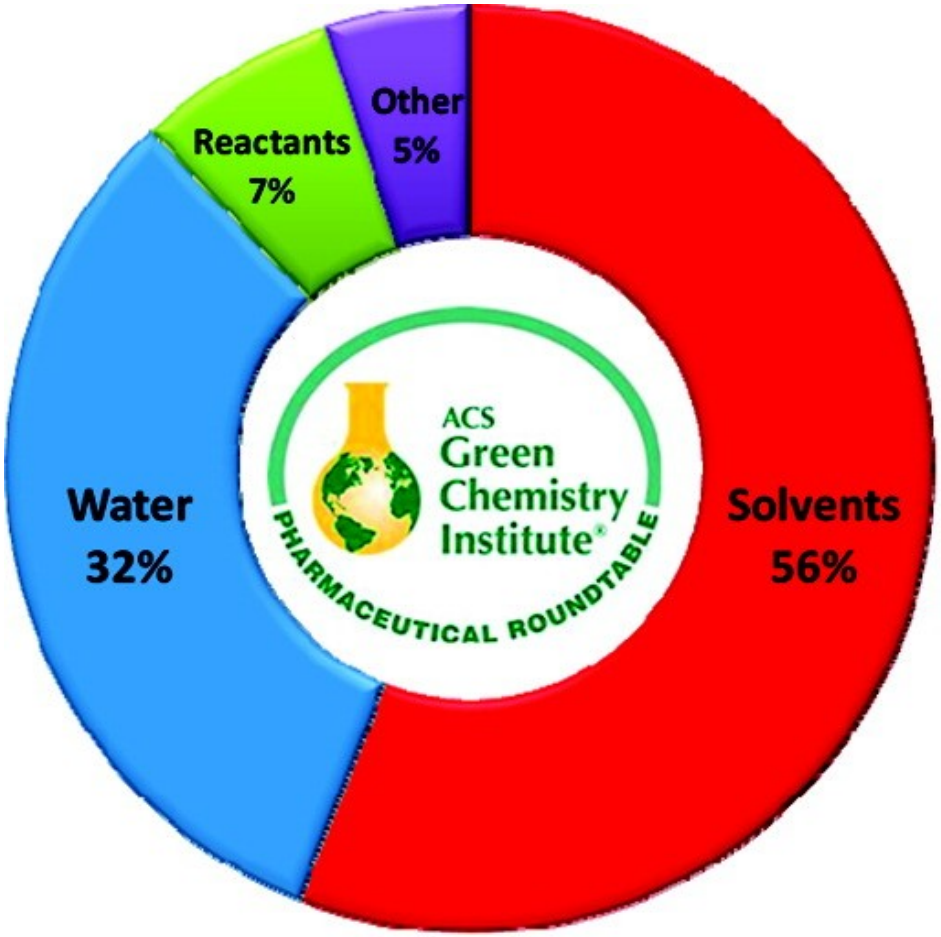
Feedstock Composition for Making APIs



Process Mass Intensity Benchmark

Jimenez-Gonzalez, C; Ponder, C.S.; Broxterman, Q.B.; Manley, J.B.
Org. Process Res. Dev. **2011,** *15*(4), 912-917

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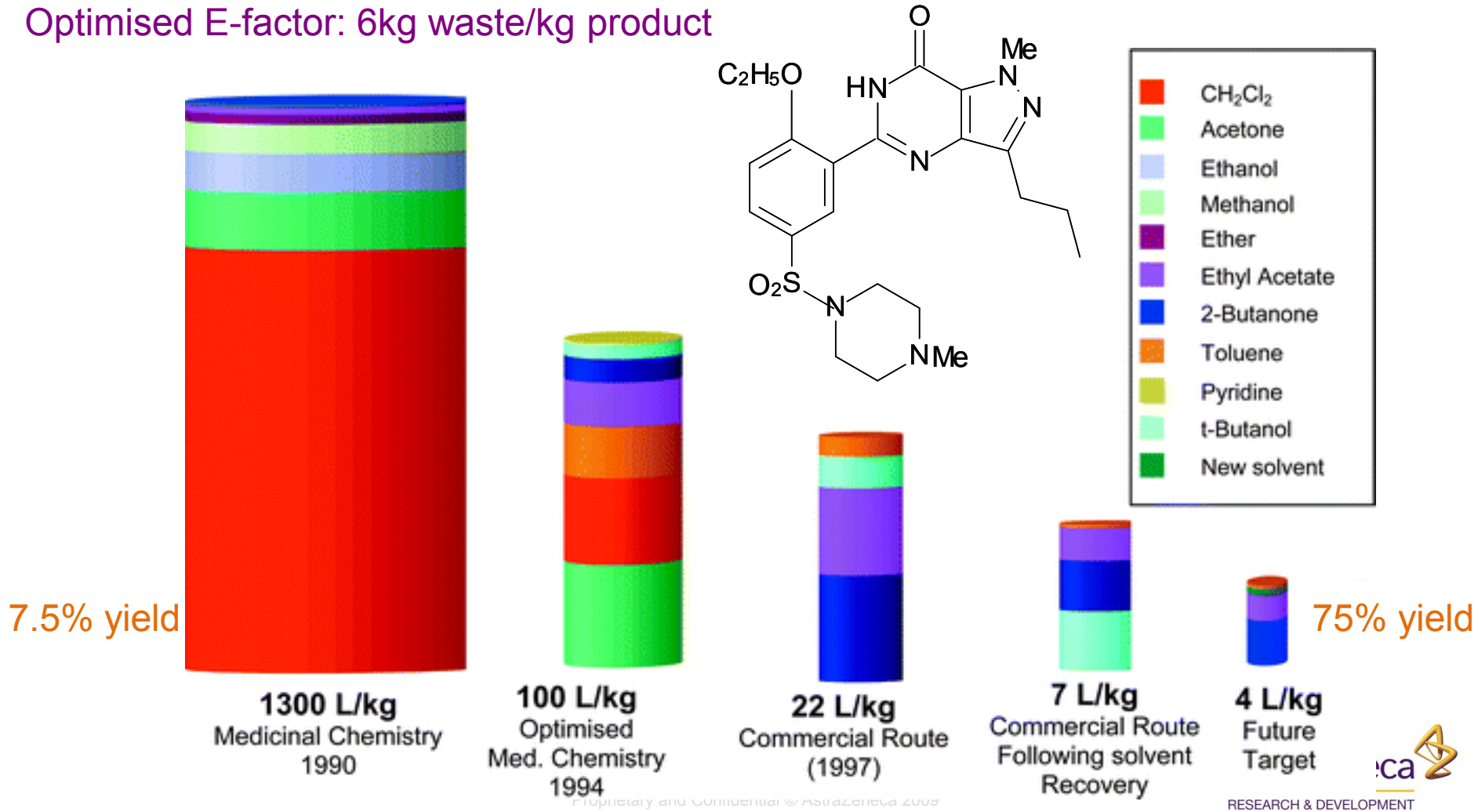
Efficiency in Solvent Utilization

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

Optimised E-factor: 6kg waste/kg product



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

Finding the Best Synthetic Route

An Overview Built on Authentic Case Stories

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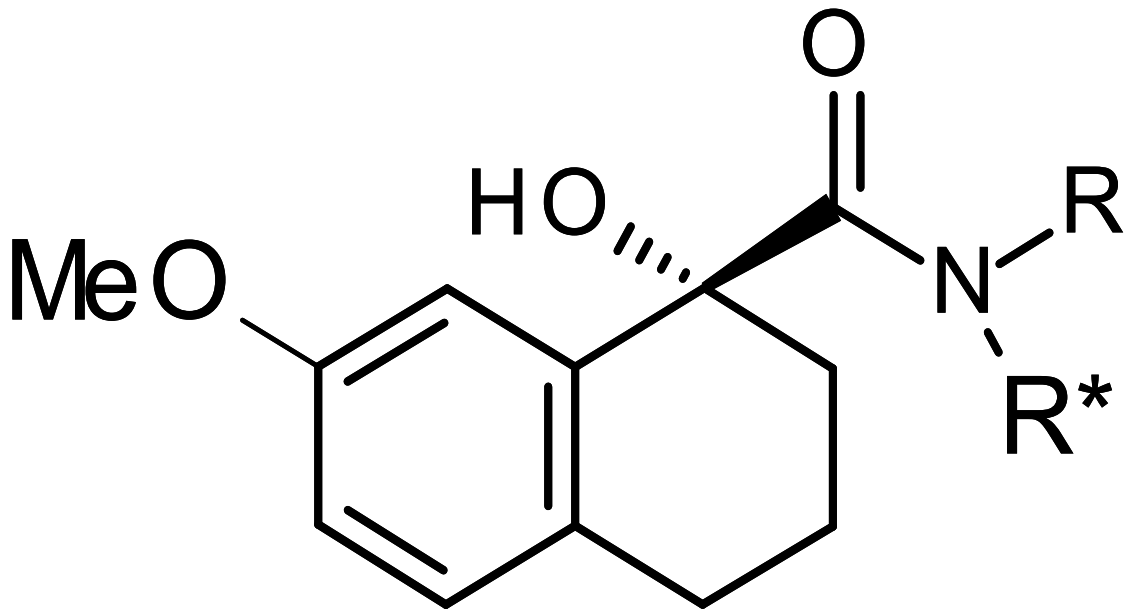
Commonly Used Transformations

Historical process data from AZ, GSK and Pfizer (including statistics from the drug development phase and full scale production)

- Heteroatom alkylation / arylation: 19%
- Deprotection: 15%
- Acylation: 12%
- C-C bond formation: 11%
- Functional group interconversion: 10%
- Reduction: 9%
- Protection: 6%
- Formation of aromatic heterocycles: 5%
- Oxidation: 4%
- Functional group addition: 3%
- Resolution: 3%
- Miscellaneous: 3%

Dugger, R.W.; Ragan, J.A.; Brown Ripin, D.H., *Org. Process Res. Dev*. **2005**, *9*(3), 253-258
Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T., *Org. Biomol. Chem*. **2006**, *4*(12), 2337-2347

Choosing the Right Synthesis



A promising class of key building blocks

Ainge, D. et al. *Org. Process Res. Dev.* **2003**, *7*(2), 198-201
Federsel, H.-J. *Acc. Chem. Res.* **2009**, *42*(5), 671-680

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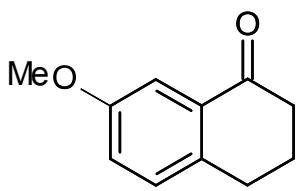
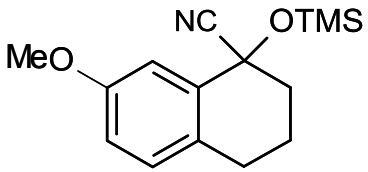
Medicinal Chemistry Route

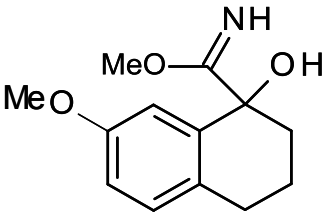


cat. $ZnCl_2$
1.1 eq. TMSCN
DCM, rt, o/n

90%



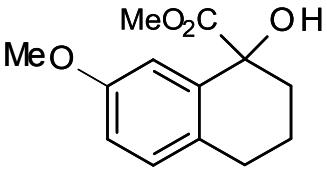
HCl/MeOH
-78 °C to rt
40 h



H_2SO_4, THF
rt, 3 days

Complex Mixture

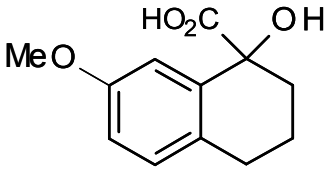
Reverse Phase HPLC



overall yield based on ketone ~10 %

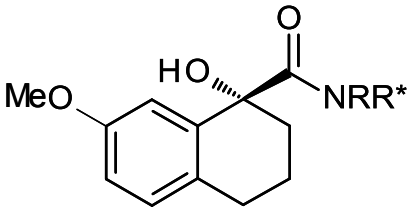
KOH, $^{i}PrOH/H_2O$
reflux, o/n

90 %



1. R*RNH, TBTU
2. Chromatography

25%



2% Overall yield from tetralone

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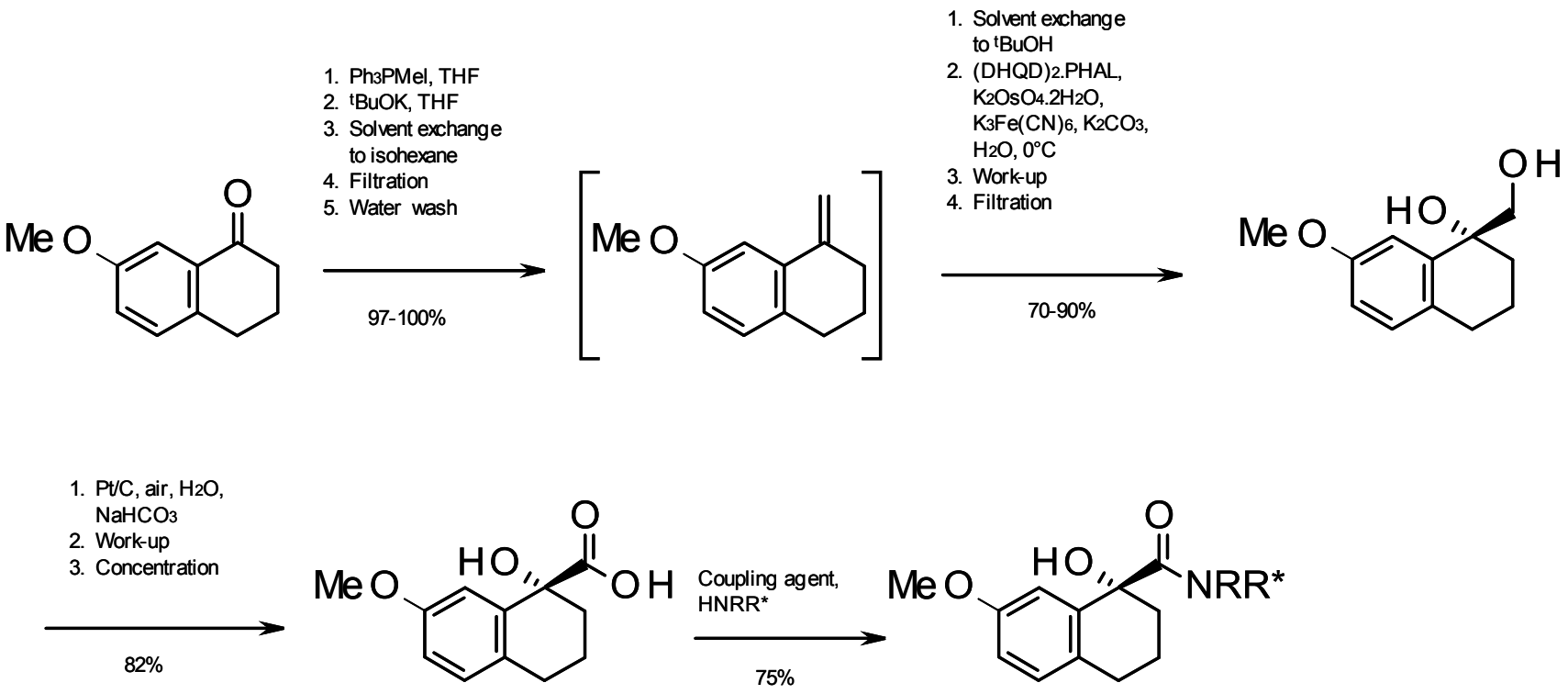
Options

Several Options for delivery on scale

- Scale-up Med Chem route “as is”
  - Long predicted manufacture times
  - Chromatographic isolation of desired enantiomer “unworkable”
  - Supply of chiral amine an issue
  - **Not viable**
- Modify Med Chem route
  - Potential for improvement of nitrile hydrolysis
  - Option to resolve racemic hydroxy ester or acid earlier in synthesis
    - Avoid chromatography in last step
  - Potential to effect asymmetric cyanohydrin reaction
    - Limited precedent with ketones
- Change route
  - Brainstorm identifies potential “winner”
  - Resource to focus on route change

A Smarter & Greener Method



42-55% Overall yield from tetralone

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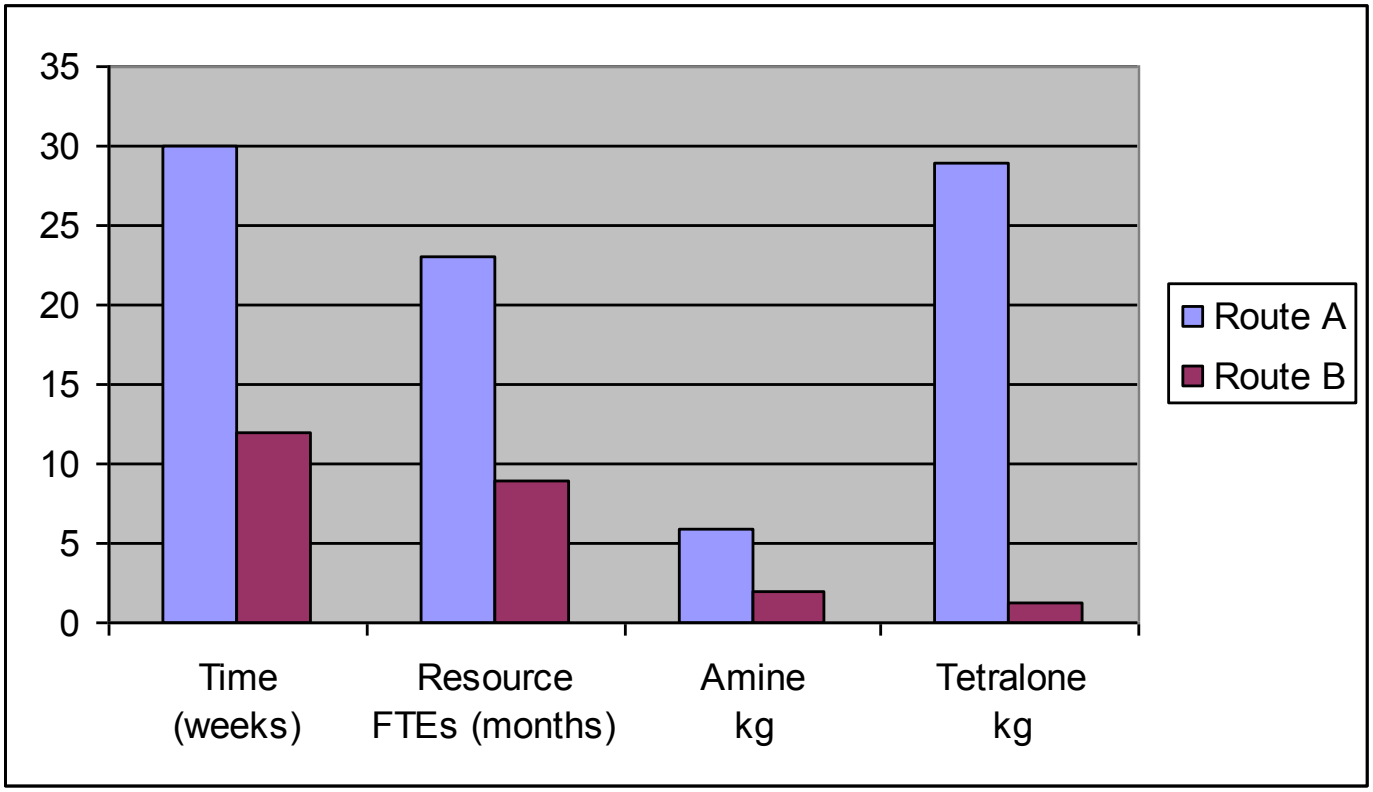
Comparing the Routes



- If project progresses, strong position to continue for next campaign
- Reduced # steps = reduced resource; can be realigned elsewhere
  - Productivity
  - Efficiency
  - Environmentally considerate
- Even if project fails at a later stage, value has been added

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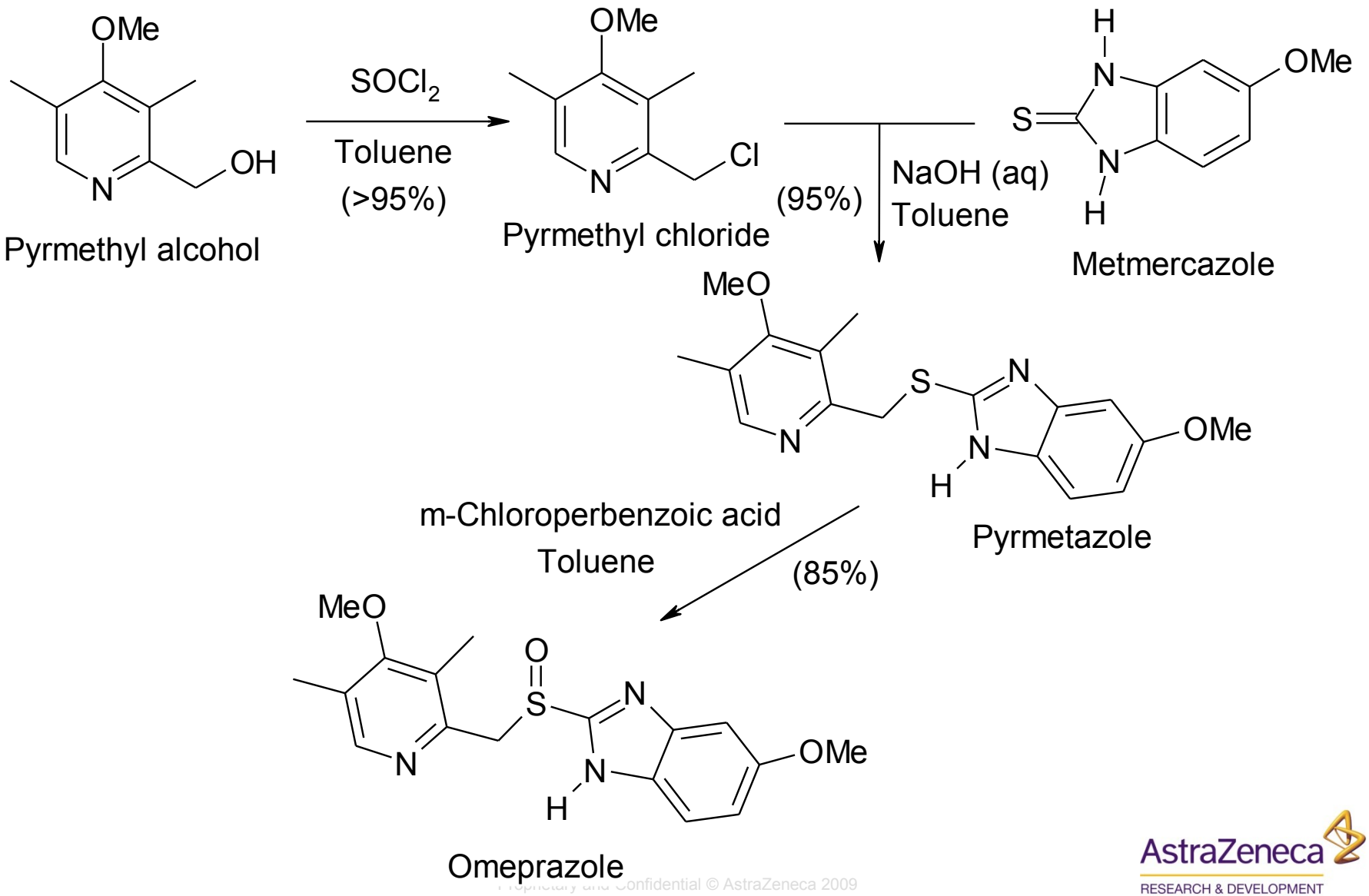
Proton Pump Inhibitors

- In 1966 research was initiated at Hässle (part of Astra) in Mölndal (close to Gothenburg) focusing on gastrointestinal diseases, especially acid secretion in the stomach (peptic ulcer, Gastroesophageal reflux disease [GERD])
- Treatment paradigms in common use
  - Antacids, e.g. Alka Selzer, Salubrin, Novalucol (neutralize excess gastric acid)
  - Surgical approaches (gastrectomy, vagotomy)
  - Novel medicines (cimetidin/Tagamet®, ranitidine/Zantac®) launched in the late 1970s; mechanism of action was antagonism of the histamine 2 receptor
- A number of compounds were identified which prevented the acid-secreting parietal cells of the stomach to elicit protons into the lumen
- Understanding biochemical concept: A specific and unique enzyme - H^+,K^+-ATPase - responsible for generating acidic conditions (Sachs et al, 1977)
- First compound to be tested in man was inefficient (worked in rat model)
- Switch to dog model and focus on structure-activity studies
  - Long-lasting action; no aute toxicity; long-term side effects; patent issues
  - In Jan 1979 first synthesis of omeprazole, which was launched in 1988 as Losec®

Large scale synthesis of omeprazole



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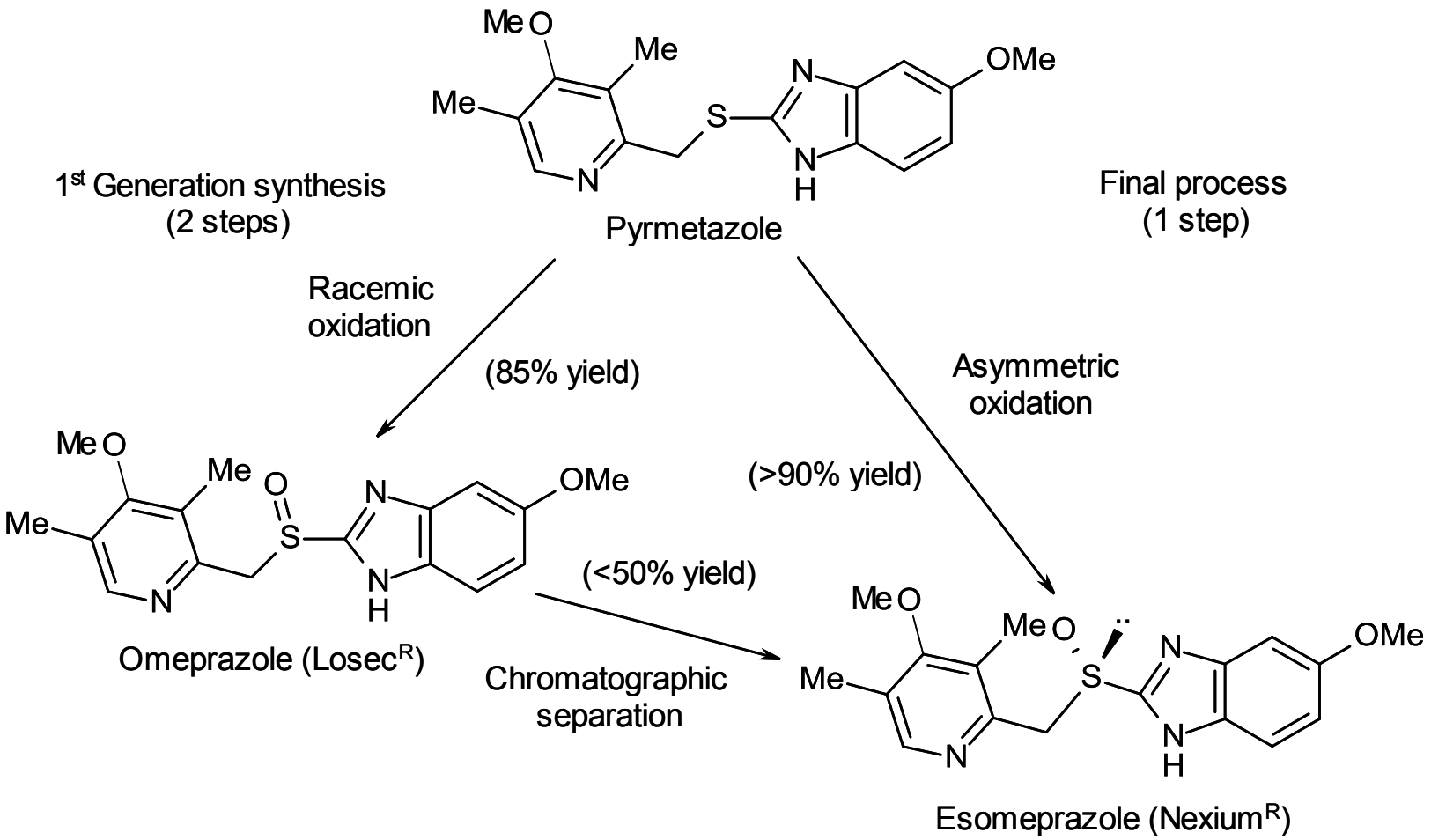
From Racemate to Single Enantiomer



Federsel, H.-J.; Larsson, M. In *Asymmetric Catalysis on Industrial Scale*. Blaser; Schmidt, eds; Wiley-VCH, Weinheim, 2004; p. 413-436

Federsel, H.-J. *Nature Rev. Drug Discov*. **2003**, *2*(8), 654-664

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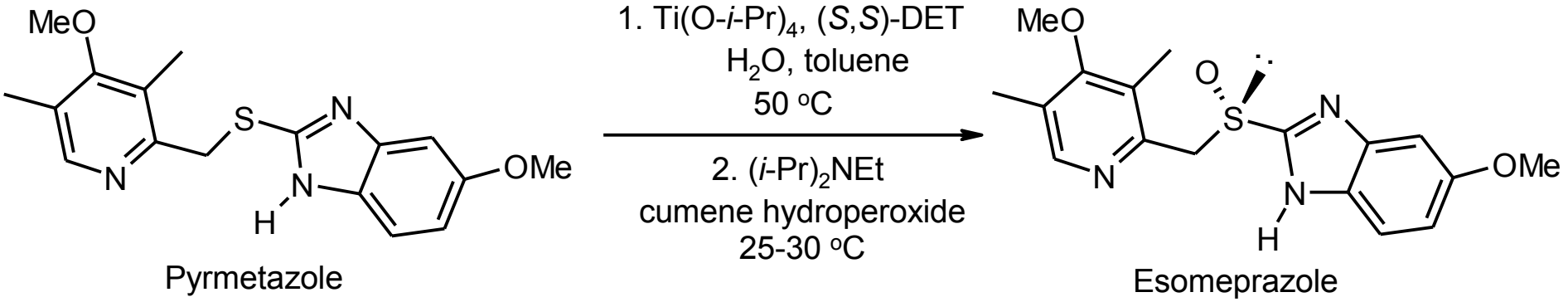
High Performing Asymmetric Catalysis



Pyrmetazole

Esomeprazole

Key features

- Hünig's base – $(i\text{-Pr})_2$NEt – essential
- Pre-formation of catalytic species required (step 1)
- Cheap oxidant
- Operative between 4-50 mol-% Ti; TON ≈4-16, TOF≈3-12 h^{-1}

Process Validation

- Multi-hundred tonnes produced in excellent yield (>90%) and quality (>90% ee)

Seenivasaperumal, M.; Federsel, H.-J. et al. *Chem. Commun*. **2007**, 2187-2189
Seenivasaperumal, M.; Federsel, H.-J.; Szabó, K.J. *Adv. Synth. Catal*. **2009**, *351*(6), 903-919

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What's Hot in Process R&D Today?

Global Trends Across the Industry

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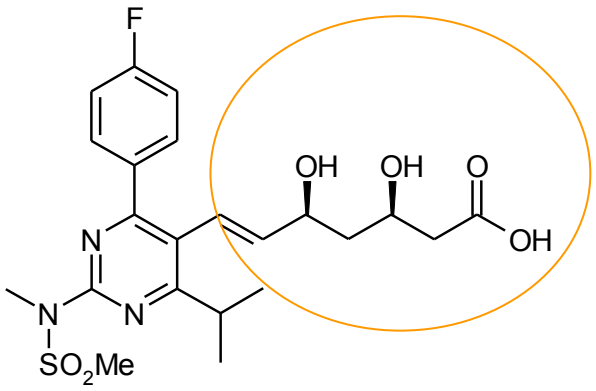
Megatrends in Process R&D

- 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 heterocyclic motifs has come of age
- Process Intensification
  - Continuous processing built on flow chemistry
    - A new paradigm with huge potential, but clear limitations
- Reaching sustainability by means of adopting Green Chemistry Principles
  - A revolutionary change in API manufacture
  - Vision: Good processes are, by default, green

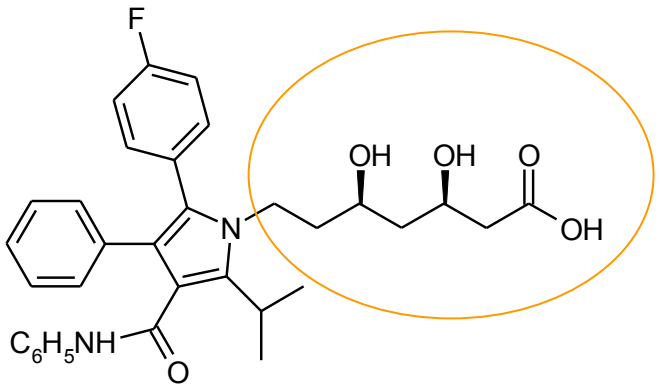
Federsel, H.-J. *Green Chem*. **2013**, *15*(11), 3105-3115

Biocatalysis: An Important Tool

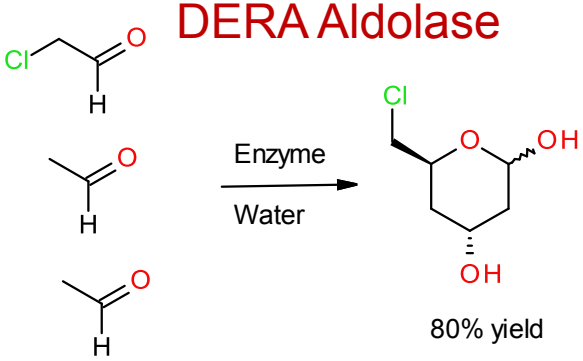
Rosuvastatin (Crestor® /AstraZeneca)



Atorvastatin (Lipitor® /Pfizer)

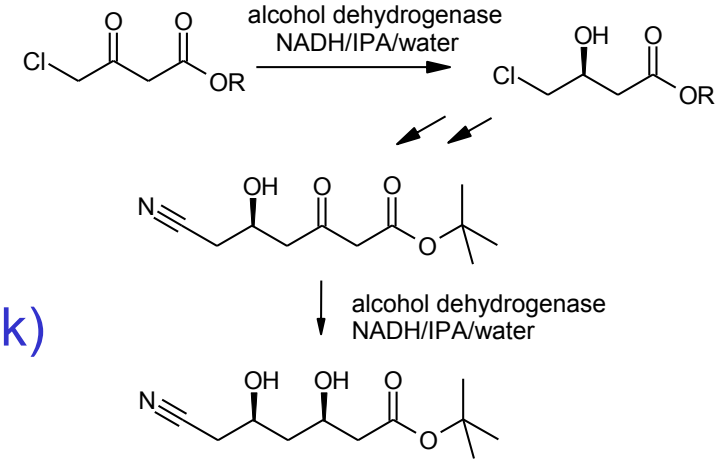


DERA Aldolase

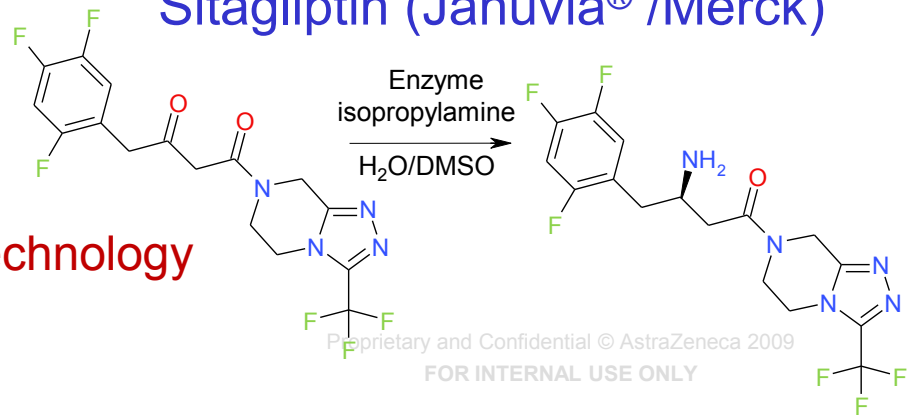


80% yield

Alcohol Dehydrogenase



Sitagliptin (Januvia® /Merck)



Transaminase technology

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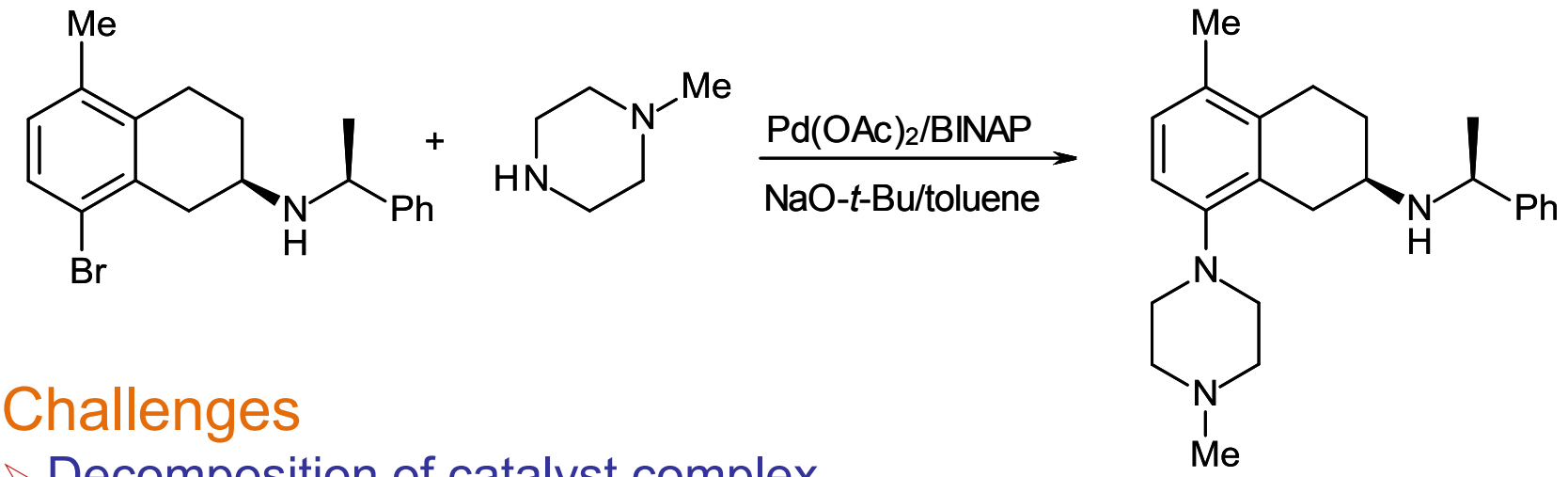
The Buchwald-Hartwig Step



Challenges

- Decomposition of catalyst complex
- Formation of debrominated by-product (*H*-analogue)

Key achievements

- 0.8 mol-% Pd used in successful pilot production (down to 0.1 mol-% on lab scale); excess BINAP and NMe-pip are required to form stable catalytic complex
- Quantitative conversion within 4h at 100°C
- Quantitative yield (process solution); max batch size 125 kg (2500 L reactor)
- Robust work-up by acidic (aq) extraction; <0.5% des-Br

Federsel, H.-J. et al. *Acc. Chem. Res*. **2007**, *40*(12), 1377-1384
Federsel, H.-J. et al. *Org. Process Res. Dev*. **2008**, *12*(3), 512-521

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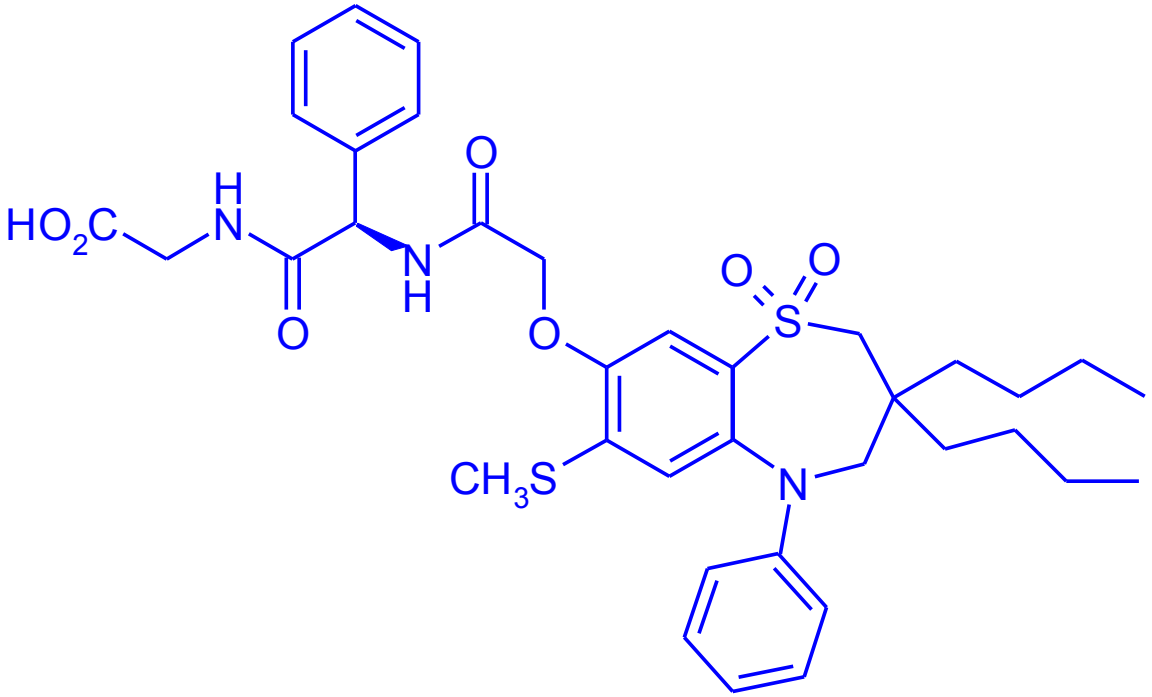
A Challenging Target



AZD7806

Intended purpose:

- Reduction of blood cholesterol levels by inhibiting ileal bile acid transfer

Molecular characteristics:

- High level of diverse functionality
- Implies large number of steps

Courtesy Adrian Clark, Pharm Dev, AZ

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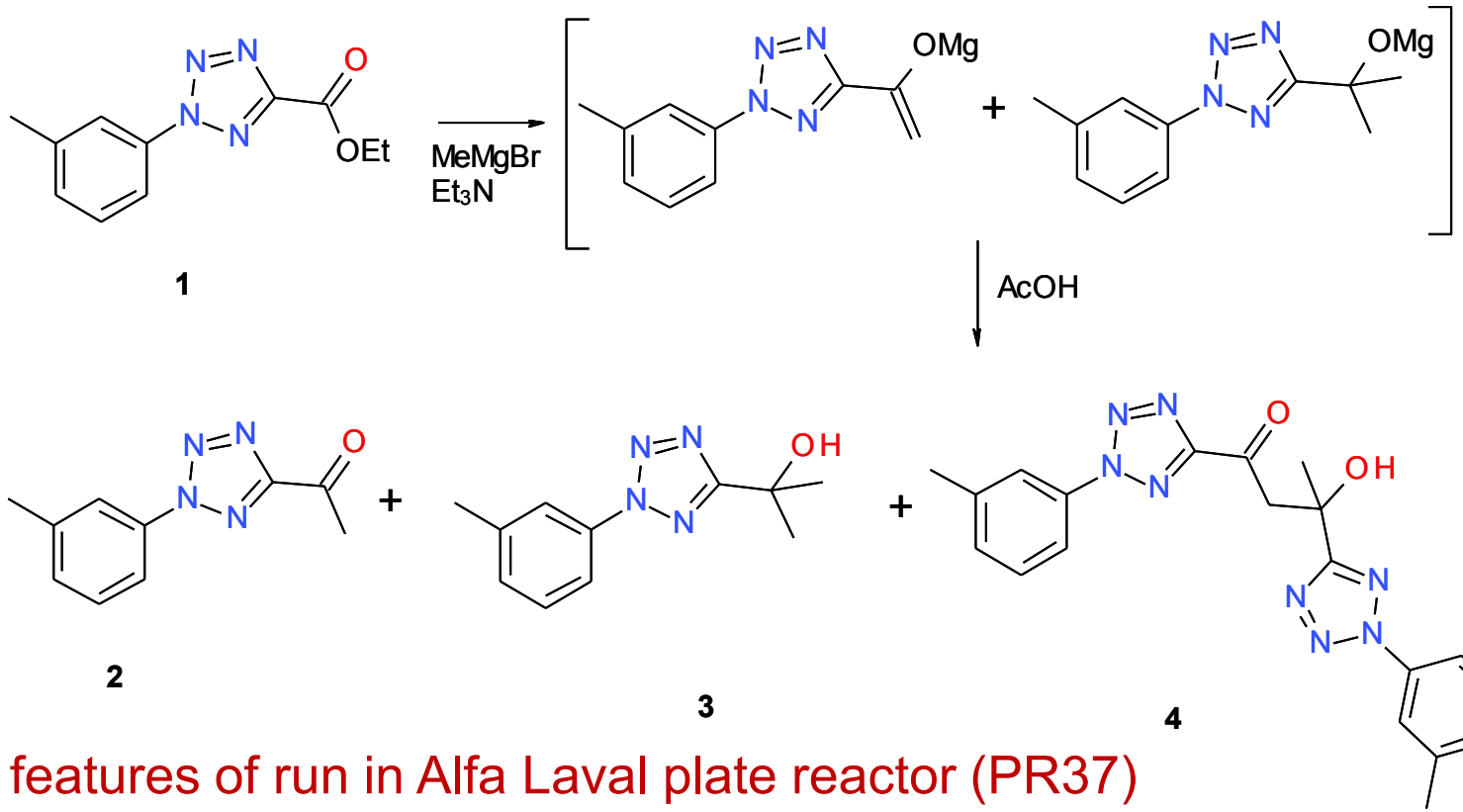
Grignard Chemistry under Flow Conditions



Main features of run in Alfa Laval plate reactor (PR37)

- 3.5 eq of *tert*-amine
- 1.7 eq MeMgBr added
- Flow rate= 72 g/min; Residence time 12 sec
- Pumping time= 92 h
- Temp= 0 to -5 °C
- HPLC analysis (area-%): **1**=4%; **2**=86.4%; **3**=6.2%; **4**=0.6%
- Amount ketone produced= 30 kg; isolated yield=60% (30% in 1000L batch)

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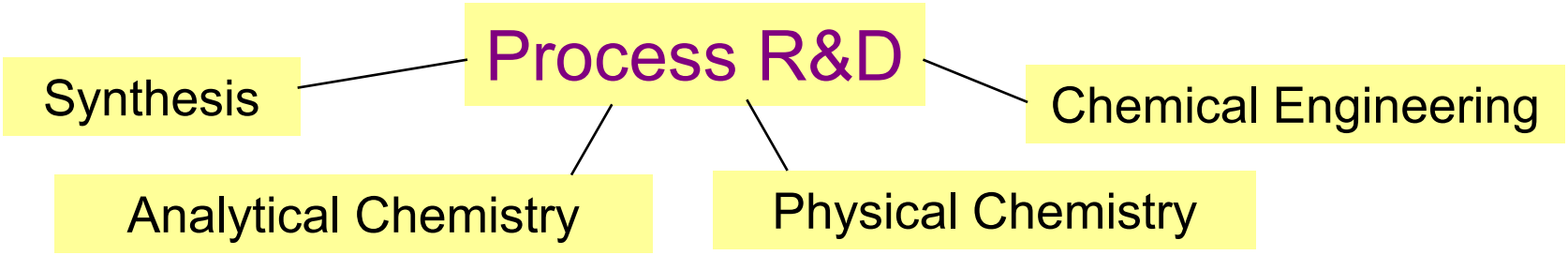
Odille, Stenemyr, Wernersson, Ridemark, Federsel, *Org. Process Res. Dev.*, manuscript

Operating Chemistry in Flow

The Alfa Laval plate reactor (PR37)

Take-home Message – Start Small, Think Big



- Goals
  - To find the best route to prepare the Candidate Drug
  - Provide material for clinical evaluation
- Key activities
  - Evaluation of possible synthetic routes, including safety and environmental aspects, patent situation, cost
  - Optimization of the most favorable route
- Miscellaneous
  - Regular interactions with other areas, e.g. quality control, formulation, clinical study leaders, bulk production

Federsel, H.-J. *Nature Rev. Drug Discov*. **2002**, *1*(12), 1013

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Want to Know More?

1) Zhang, T. Y., Process Chemistry: The Science, Business, Logic, and Logistics, *Chem. Rev*. **2006**, *106*(7), 2583-2595
2) Federsel, H.-J., Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective, *Acc. Chem. Res*. **2009**, *42*(5), 671-680
3) Federsel, H.-J., Process R&D Under the Magnifying Glass: Organization, Business Model, Challenges, and Scientific Context, *Bioorg. Med. Chem*. **2010**, *18*(16), 5775-5794

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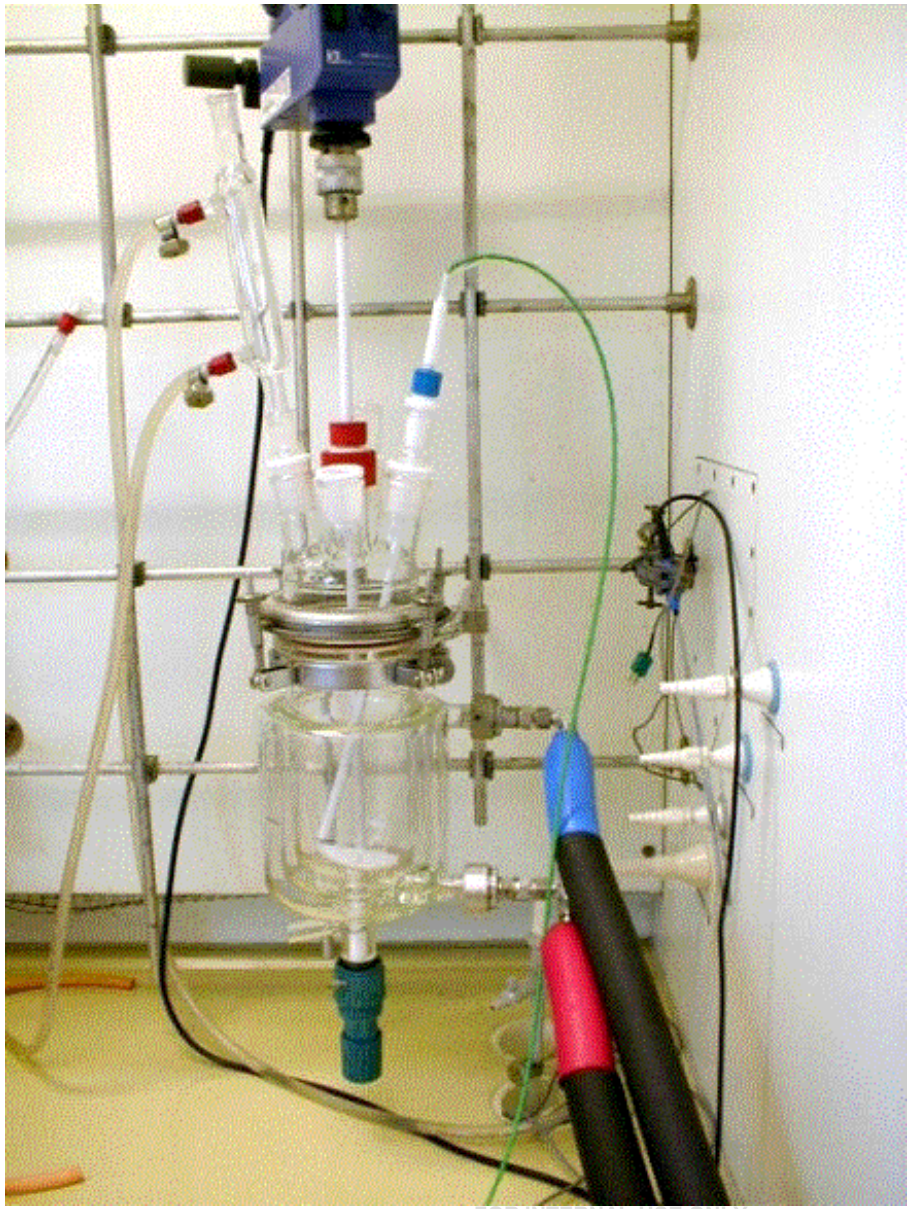
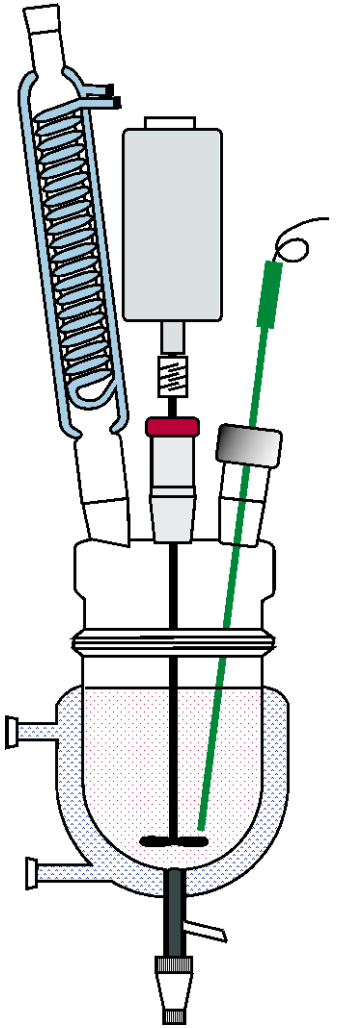
Typical Laboratory Glass-ware





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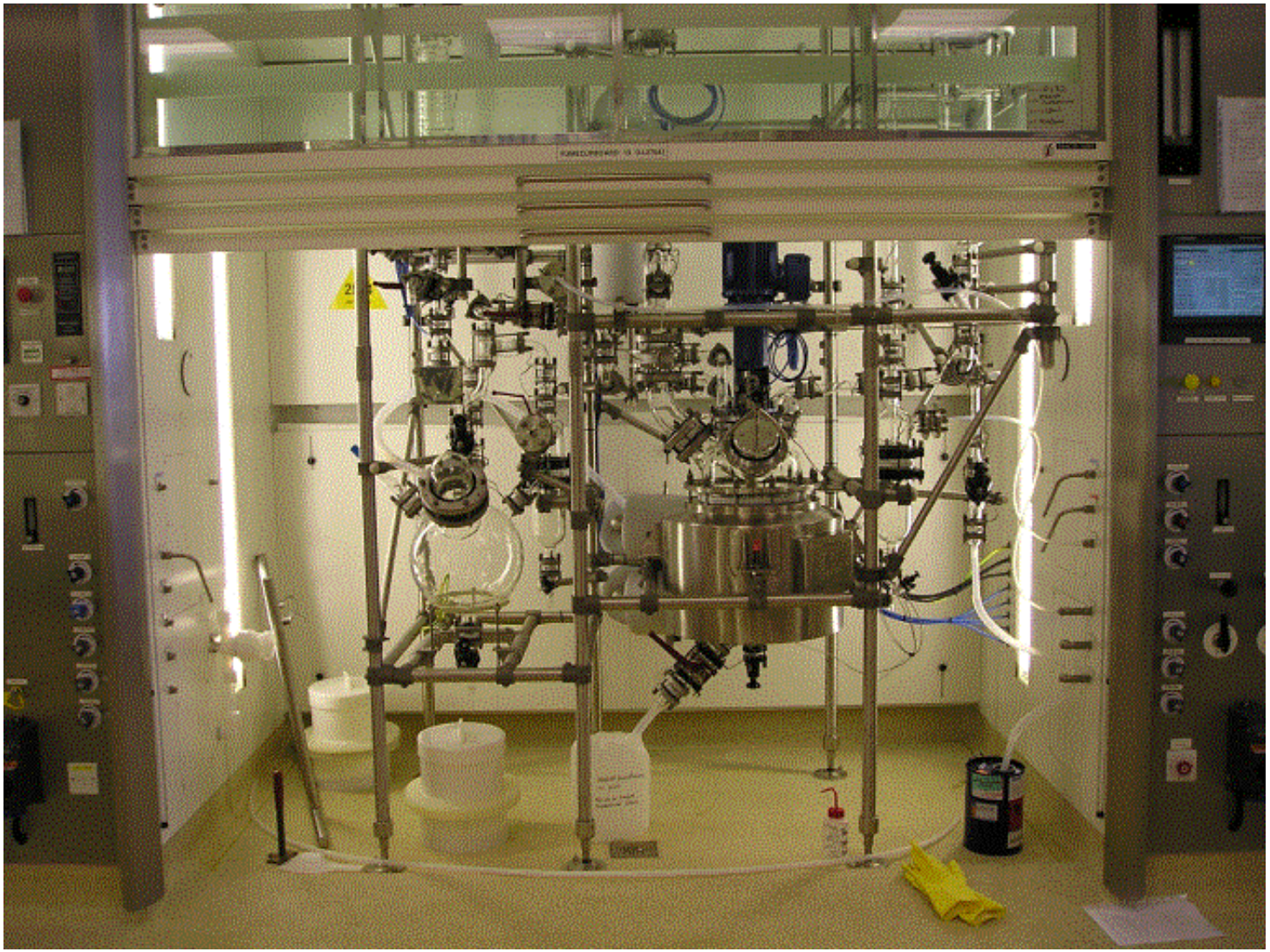
Large-Scale Laboratory (20L)



Pilot Plant

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