POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Process Redesign of Pharma Synthesis.

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Dipartimento CMIC “Giulio Natta”
https://iscamapweb.chem.polimi.it/citterio/it/education/course-topics/

Pharmaceutical Industry.

- Major commercial sector in EU Region
  - ✓ Italy is known to have long tradition as medicine chest
- Biotechnology and biochemical synthesis
  - ✓ Genetic engineering/Fermentation
- Organic synthesis
  - ✓ Chemical reaction/purification
- API (Active Pharmaceutical Ingredient)
  - Active principle within the pill
- 2012, $325.8 Billion sales prescription drugs*
  - $112 Billion sales for top 5 drugs classes
- Energy usage is between 50-300 MJ·kg^{-1} API
- Solvent usage is around 300 kg·kg^{-1} API

*Michael Bartholow, PharmD, CACP, 2012_U.S.Medicines_Report.pdf

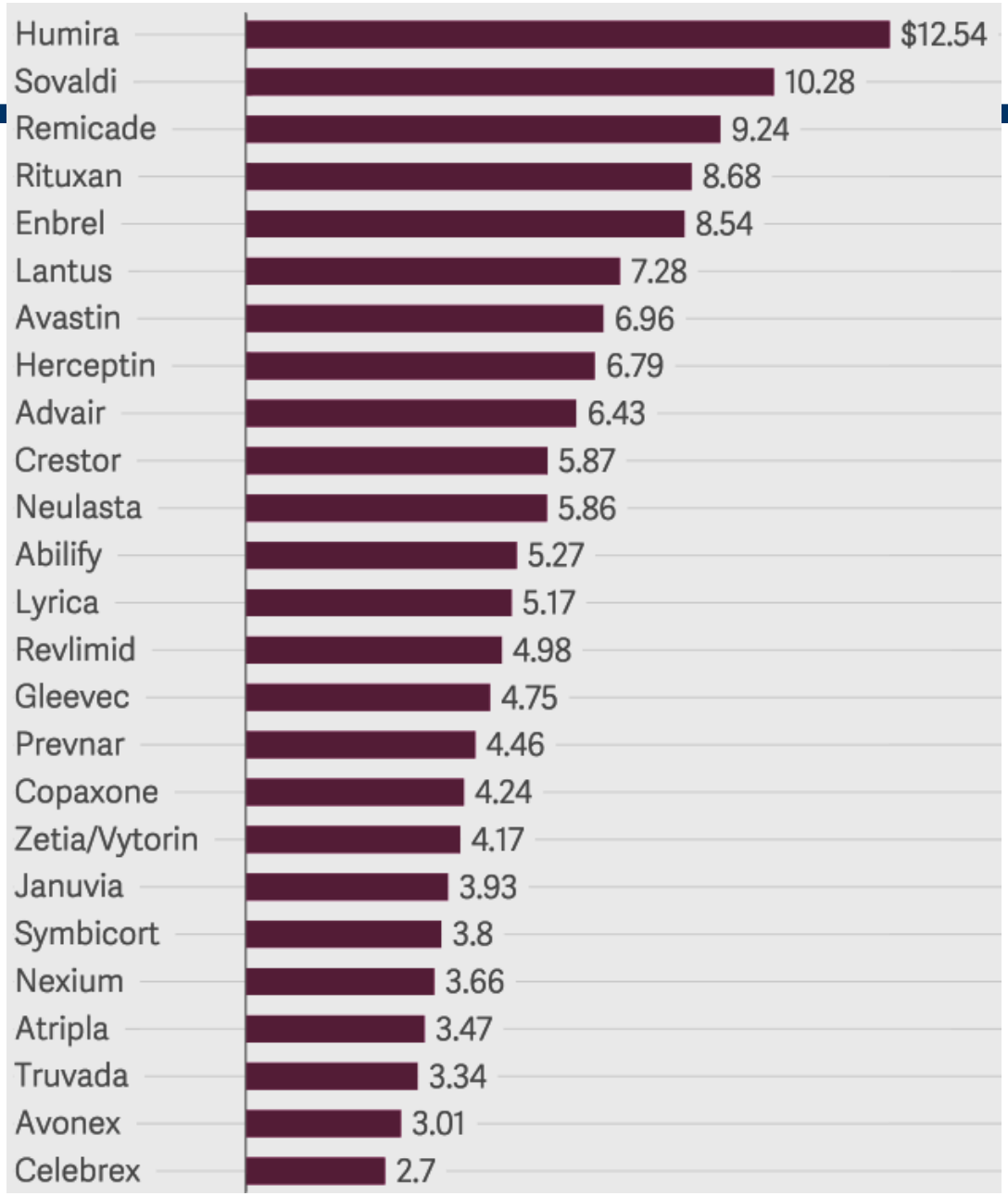
Top 20 Products of 2012 by Total Dollars.

Rank	Product	Manufacturer	Sales ($)	Rank	Product	Manufacturer	Sales ($)
1	Nexium	AstraZeneca	5,989,000,000	11	Singulair	Merck & Company	3,300,000,000
2	Abilify	Otsuka America	5,870,000,000	12	Rituxan	Genentech	3,197,000,000
3	Crestor	AstraZeneca	5,092,000,000	13	Plavix	Bristol-Myers Squibb/sanofi-aventis	2,971,000,000
4	Advair Diskus	GlaxoSmithKline	4,889,000,000	14	Atripla	Bristol-Myers Squibb Gilead	2,899,000,000
5	Cymbalta	Lilly	4,720,000,000	15	Spiriva Handihaler	Boehringer Ingelheim	2,833,000,000
6	Humira	Abbvie	4,609,000,000	16	Oxycontin	Purdue Pharma	2,808,000,000
7	Enbrel	Amgen	4,337,000,000	17	Januvia	Merck & Company	2,670,000,000
8	Remicade	Centocor	3,876,000,000	18	Avastin	Genentech	2,661,000,000
9	Copaxone	Teva CNS	3,581,000,000	19	Lantus	sanofi-aventis	2,327,000,000
10	Neulasta	Amgen	3,460,000,000	20	Truvada	Gilead Sciences	2,305,000,000

Michael Bartholow, PharmD, CACP, 2012_U.S.Medicines_Report.pdf

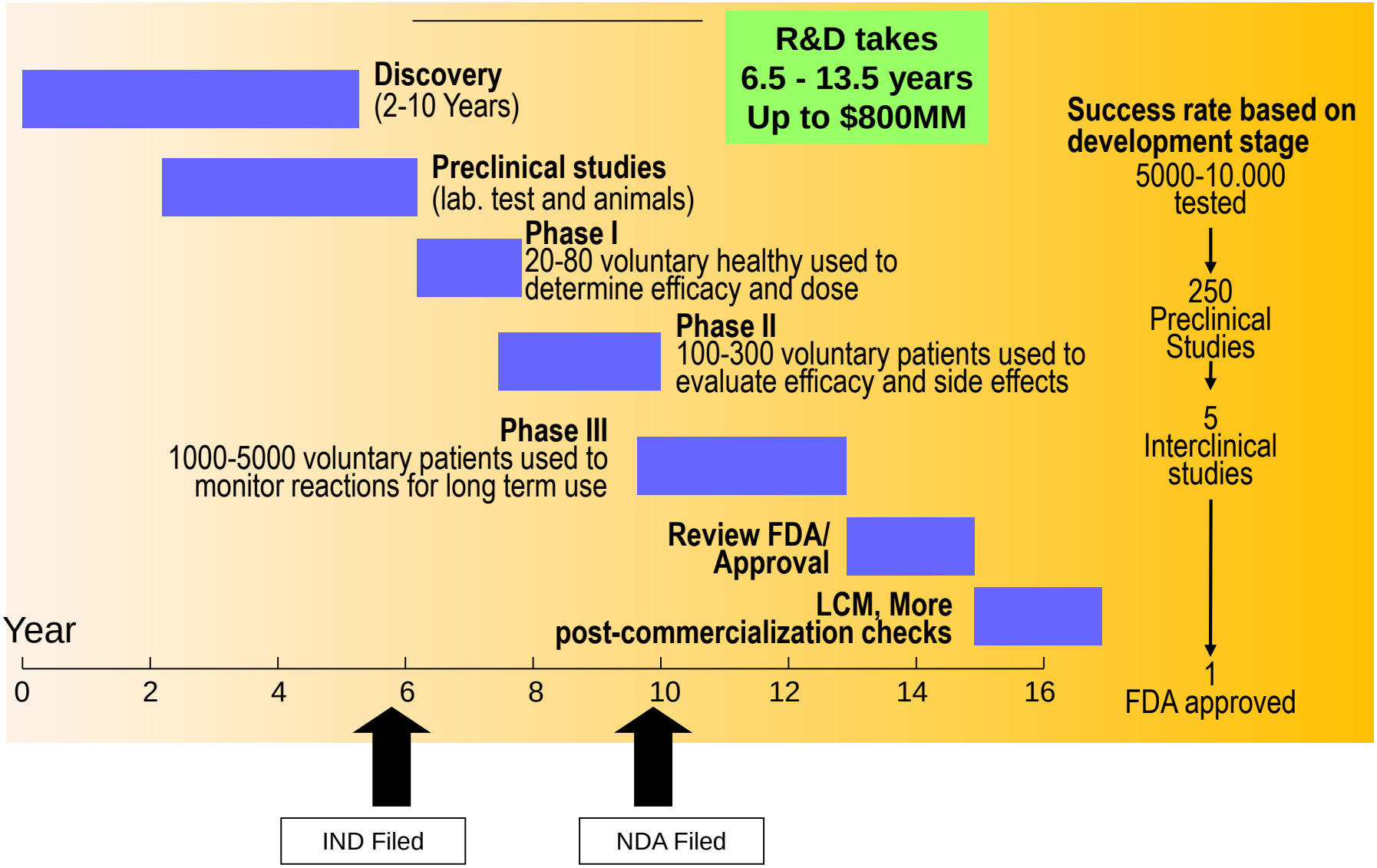
The Best Selling Drugs in the Word.

2014 Sales in billions

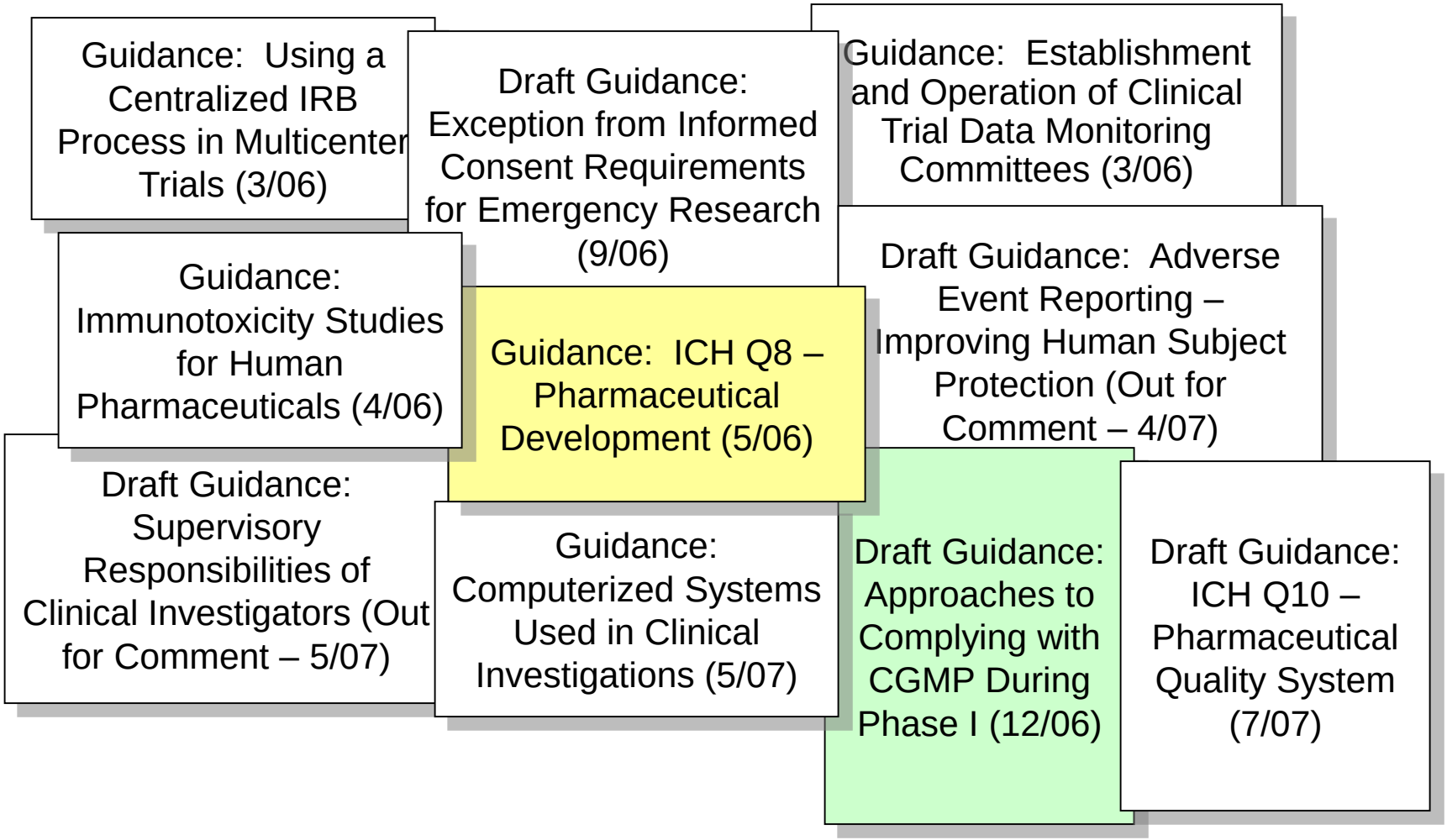


http://qz.com/349929/best-selling-drugs-in-the-world/

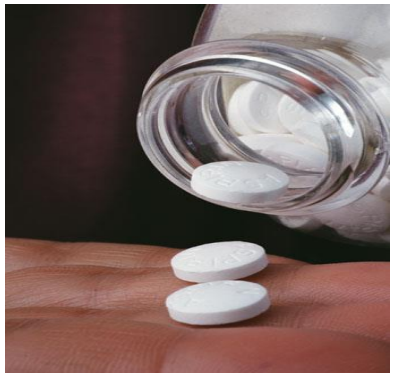
Success Rate of a Pharmaceutical Compound on Development Stage.



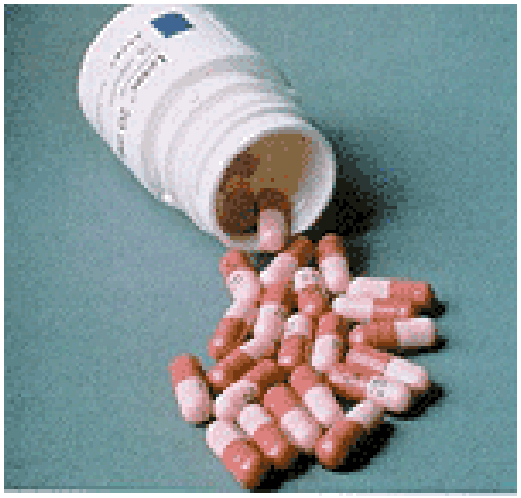
The Changing Landscape of Development Compliance.



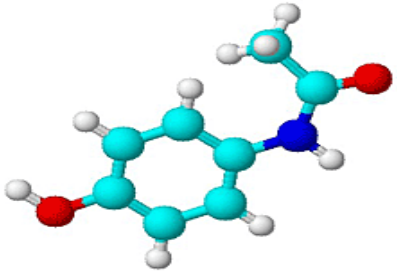
The Changing Face of Drugs.



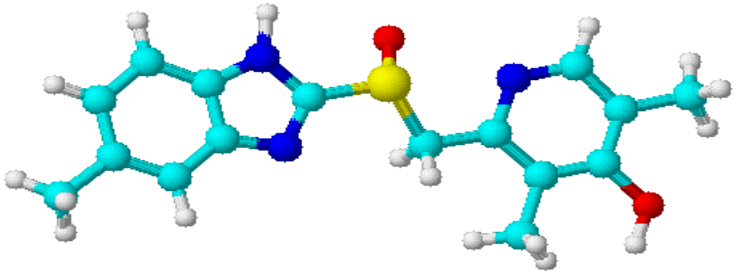
Aspirin



Losec



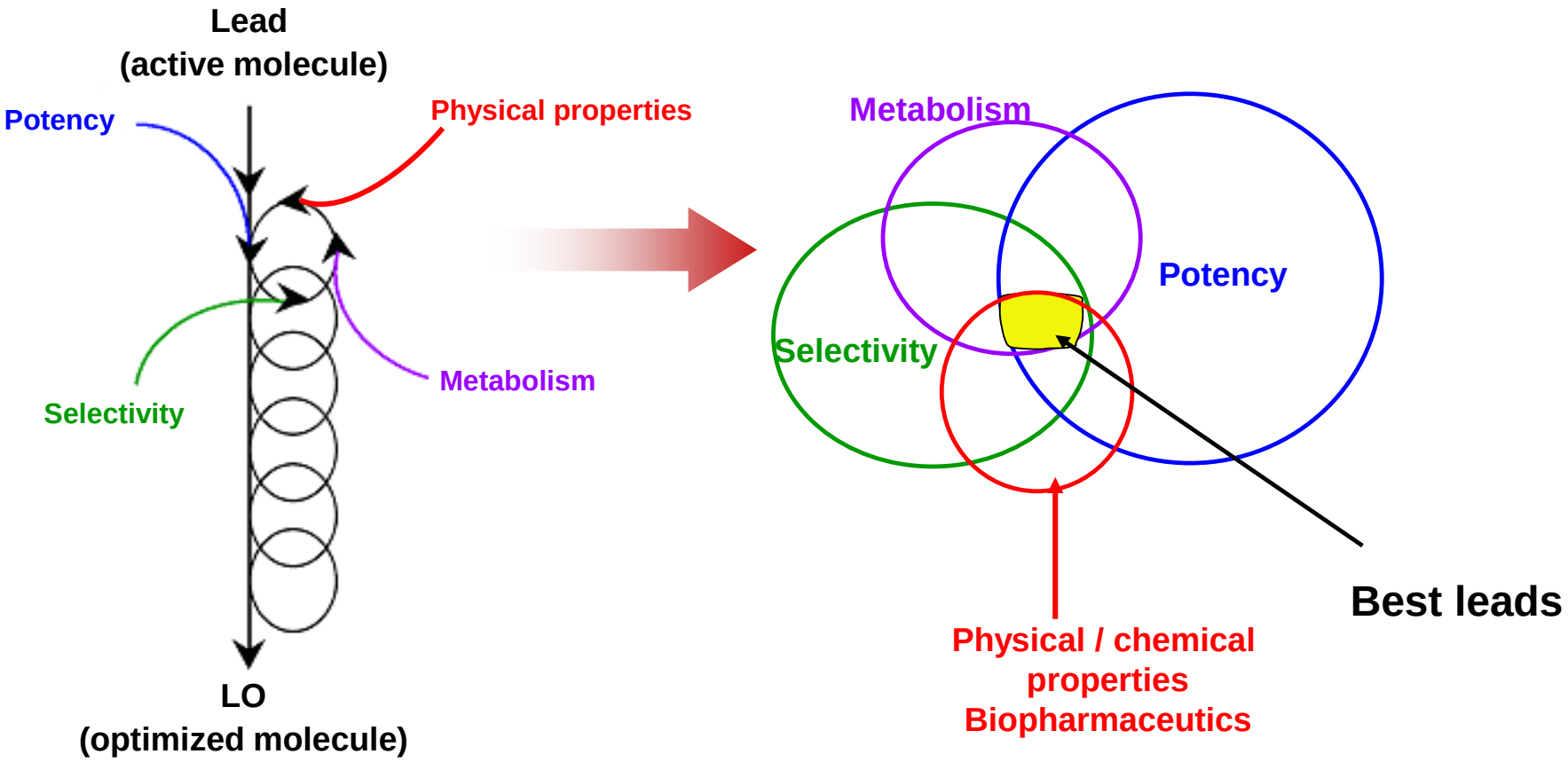
Paracetamol



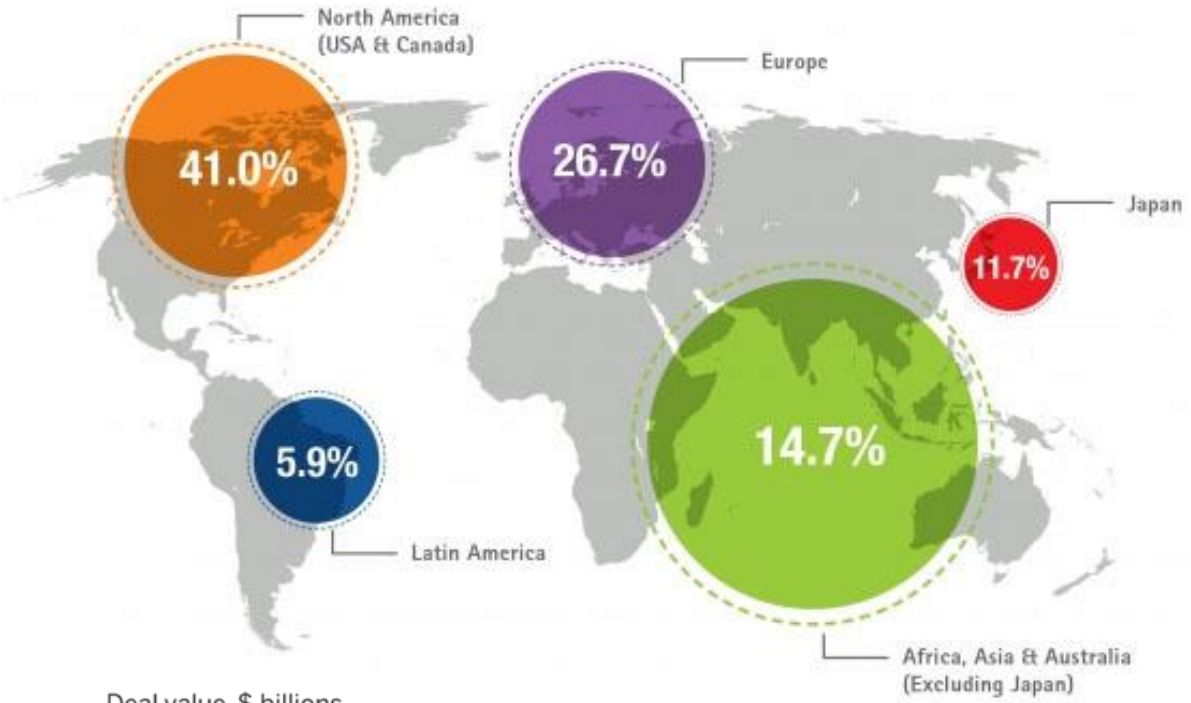
Active price : 5 $·kg^{-1}

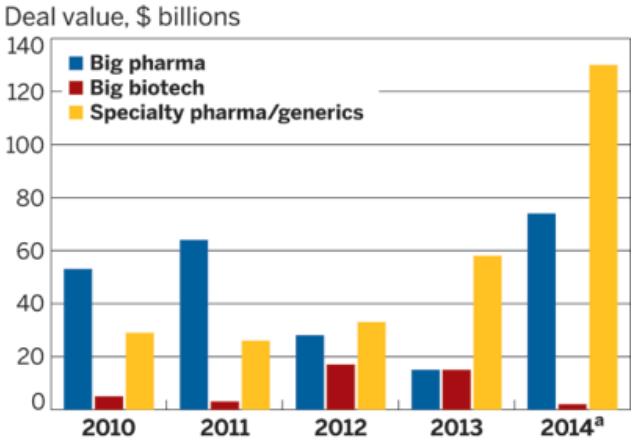
Active Price : 500 $·kg^{-1}

Candidate Selection: Building in “Developability”.



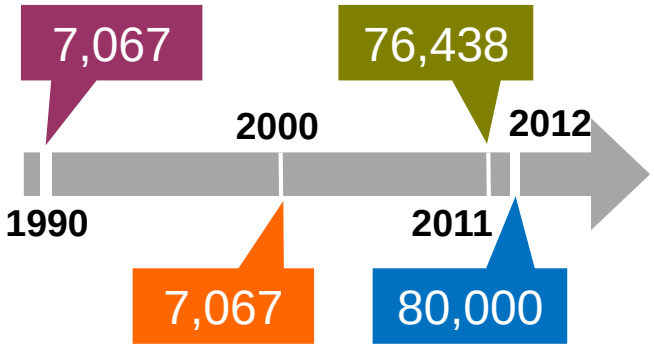
Breakdown of the World Pharmaceutical Market (2012 sales).



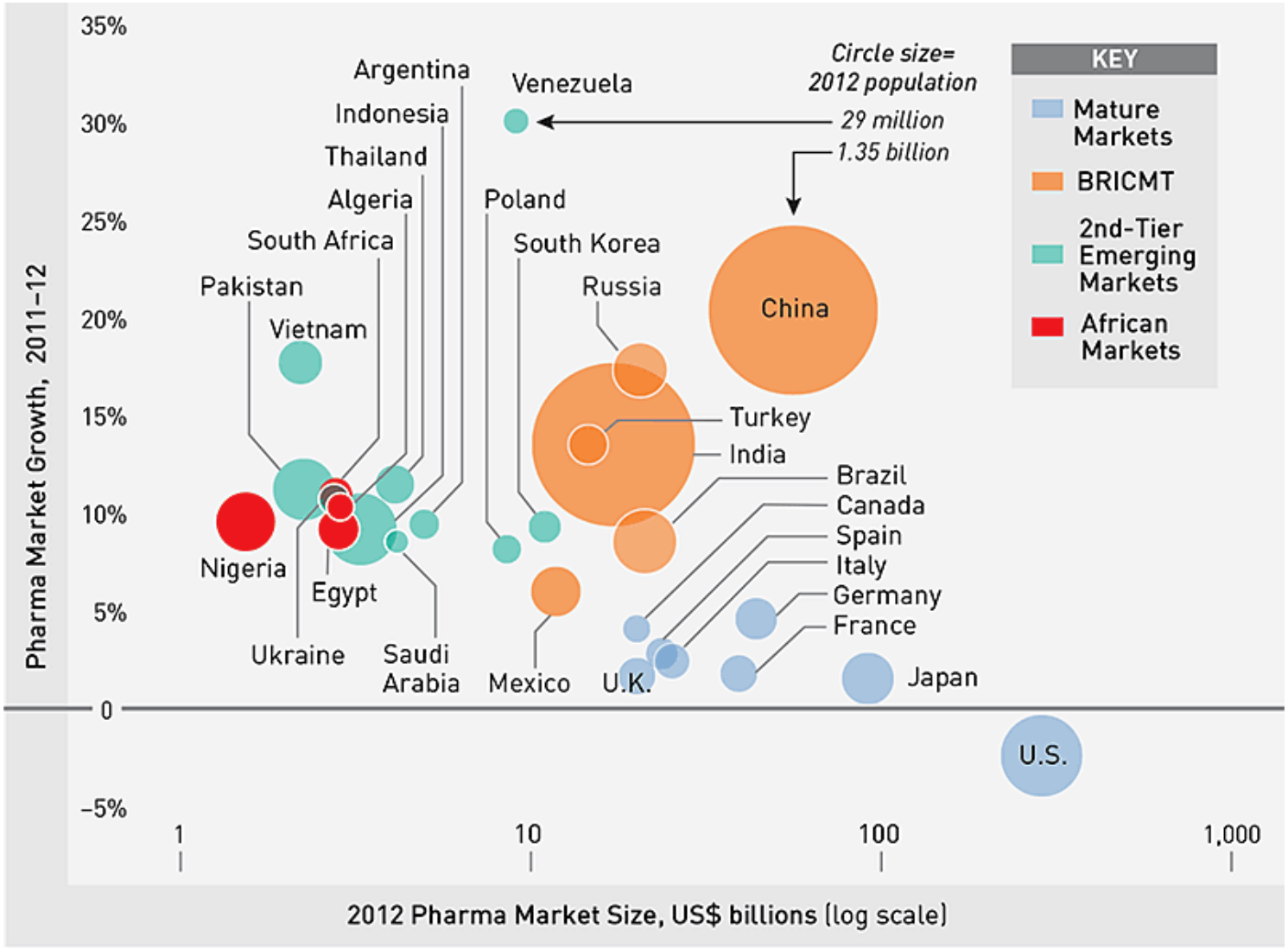


In EU pharmaceutical trade Surplus was estimated at

€ 80 BILLION

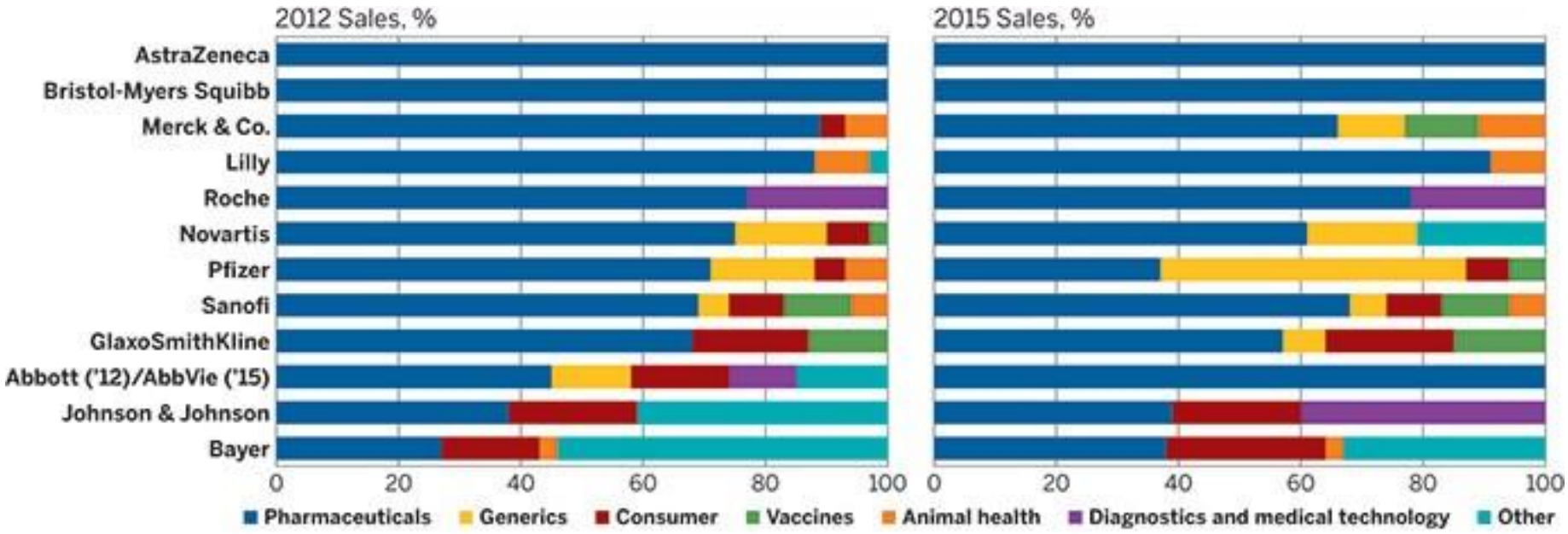


The Global Pharmaceutical Market, 2012



Source: M. Buente, S. Danner, S. Weissbäcker, C. Rammé, Booz & Company, 2013.

PORTFOLIO SHUFFLE
of Main Pharmaceutical Industries.



Through swaps and divestitures, companies are rationalizing portfolios to focus on fewer businesses. NOTE: Figures for 2015 are based on pro forma sales estimates, including deals announced in 2014.

SOURCE: Ernst & Young

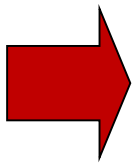
Pharmaceutical Trend.

- NEW PRODUCT DEVELOPMENT CYCLE EXTENDING
- NEW PRODUCT (NME) LAUNCHES DECREASING
- PATENT EXPIRY OF BLOCK BUSTERS PEAKING (2011-12)
- SHAREHOLDER EXPECTATIONS STILL HIGH
- MANUFACTURING COST INCREASING AND NOW LARGER THAN RESEARCH & DEVELOPMENT




Primary MFG Trends.

- MORE COMPLEX MOLECULES
- PURITY & HYGIENE
- CROSS CONTAMINATION (FDA)
- ENVIRONMENTAL CONTROL (EA/HSE)
- PRODUCT STEWARDSHIP (NGO'S)



COST ESCALATORS

Manufacturing Issues

- Batch-based processes
- Multi-step synthesis, transformations – intermediates
- Isolations (purification)
- Extensive use of multiple organic solvents and reagents – varying degrees of toxicity
- Limited health data on intermediates

Manufacturing Issues.

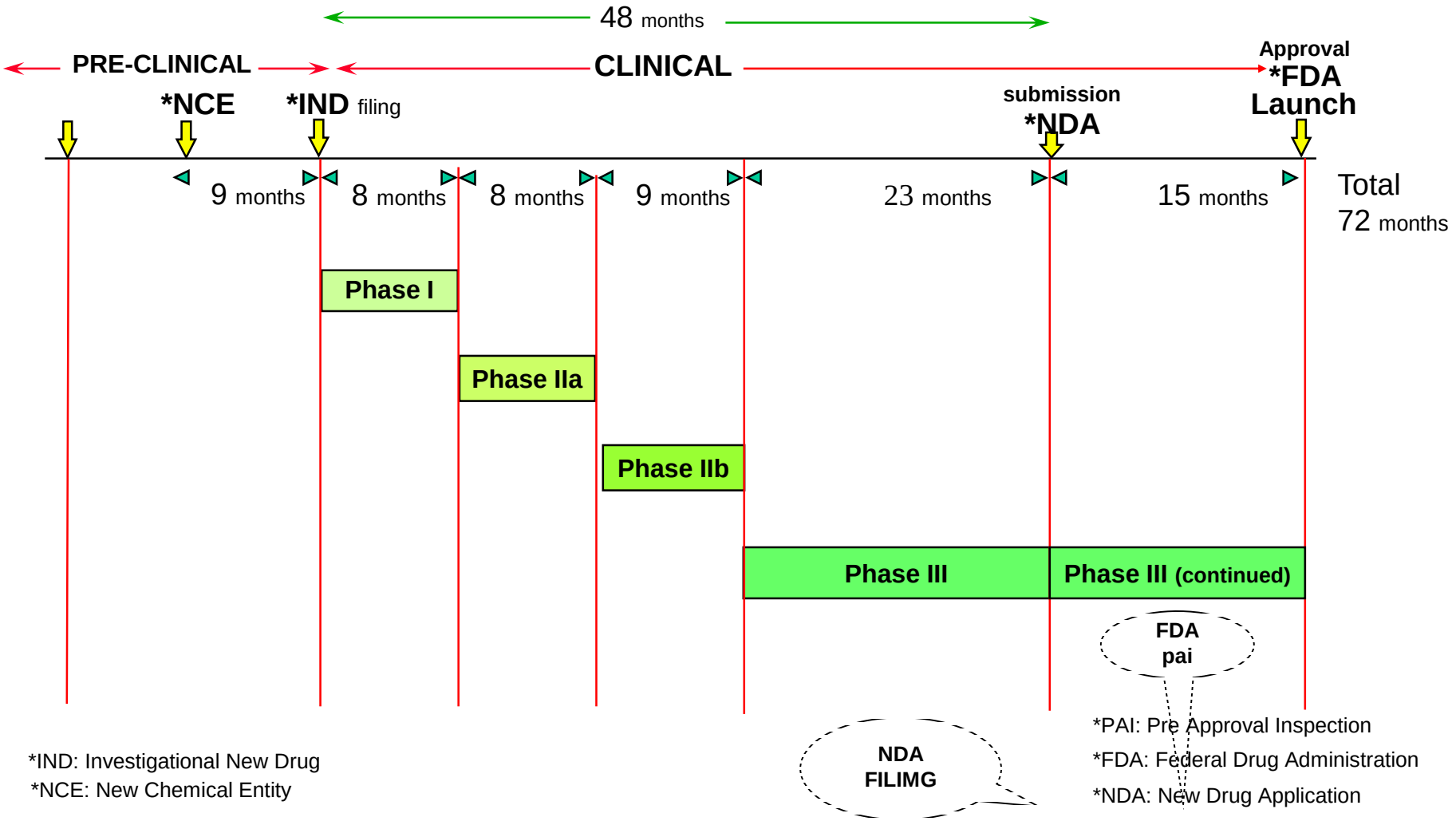
- Processes – solid/liquid – filtration, drying, etc.
- Purity and yield
- 7-11 years between development and manufacture – Regulatory steps (Phase I-III)
- 10% success rate for new drug development
- Outsourcing process steps
- Once process is approved by FDA, any changes are hard to implement.

Drug Development Process: Clinical Phases.

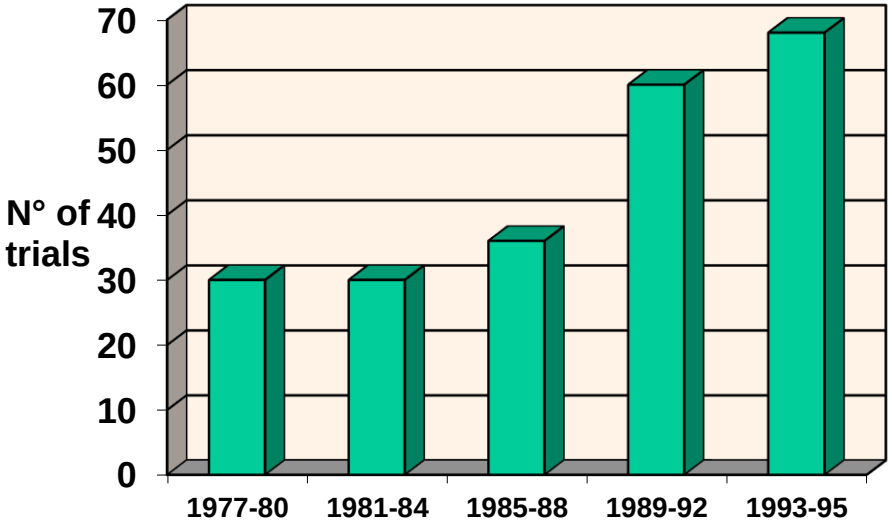
Following animal studies, compounds are tested in human populations:

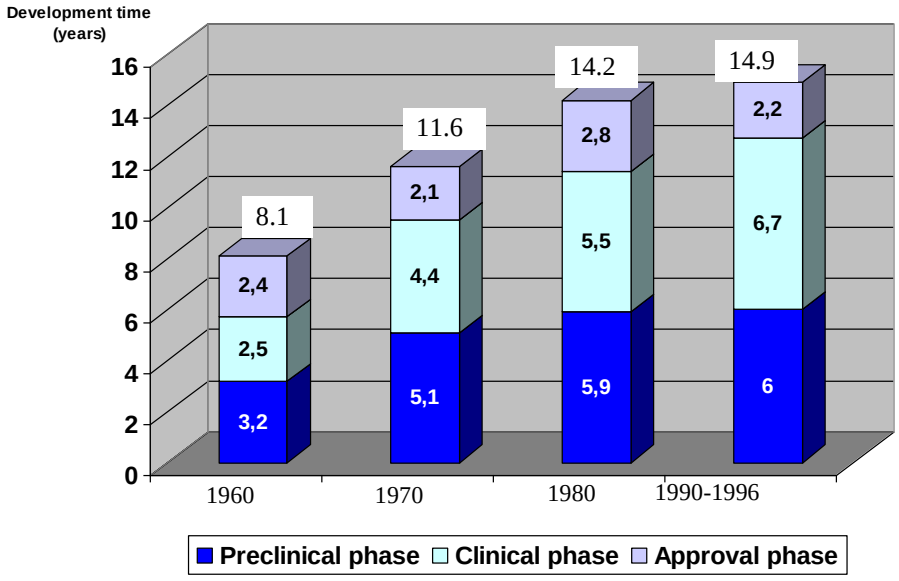
PHASE	DETAILS
I	• Safety and tolerance of drug • Pharmacokinetics parameters • ADME: Adsorption, Distribution, Metabolism, & Excretion • Small population of healthy, paid volunteers
IIa	• Proof of concept • Final decision on formulation • Tens of patients
IIb	• Determination of active dose • Double blind trials vs. comparators • Hundreds of patients
IIIa	• Efficacy (1 dose) on limited number of indications vs. one comparator • Thousands of patients (2,000 – 10,000)
IIIb	• Extension of indications (e.g., quality of life, comparison to other marketed therapeutics)
IV	• Long-term safety and efficacy of launched product

Drug Development Process: 5-7 Years Between Project Start and Launch.



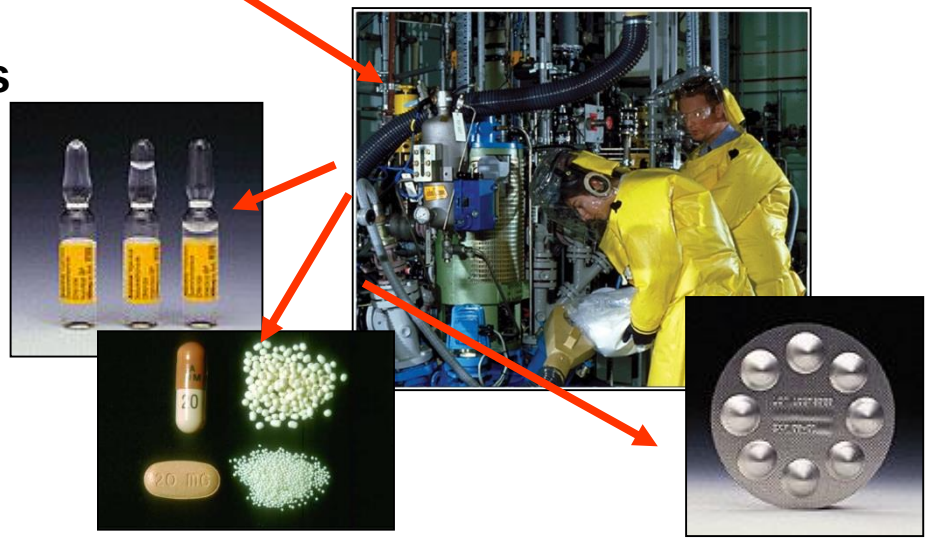
Number of Trials and Development Time of New Drugs.



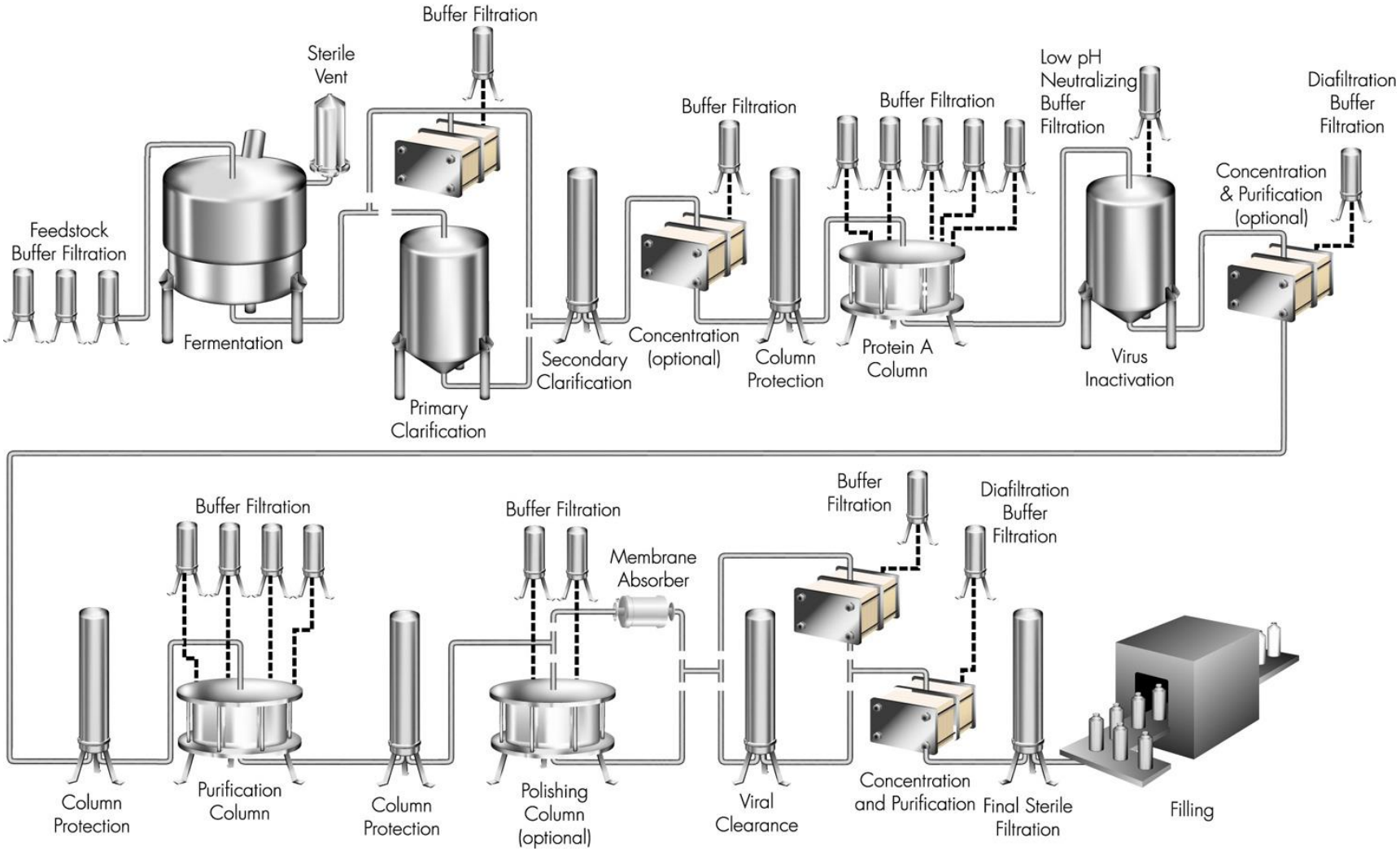


Chemical Engineering: Adjustment.

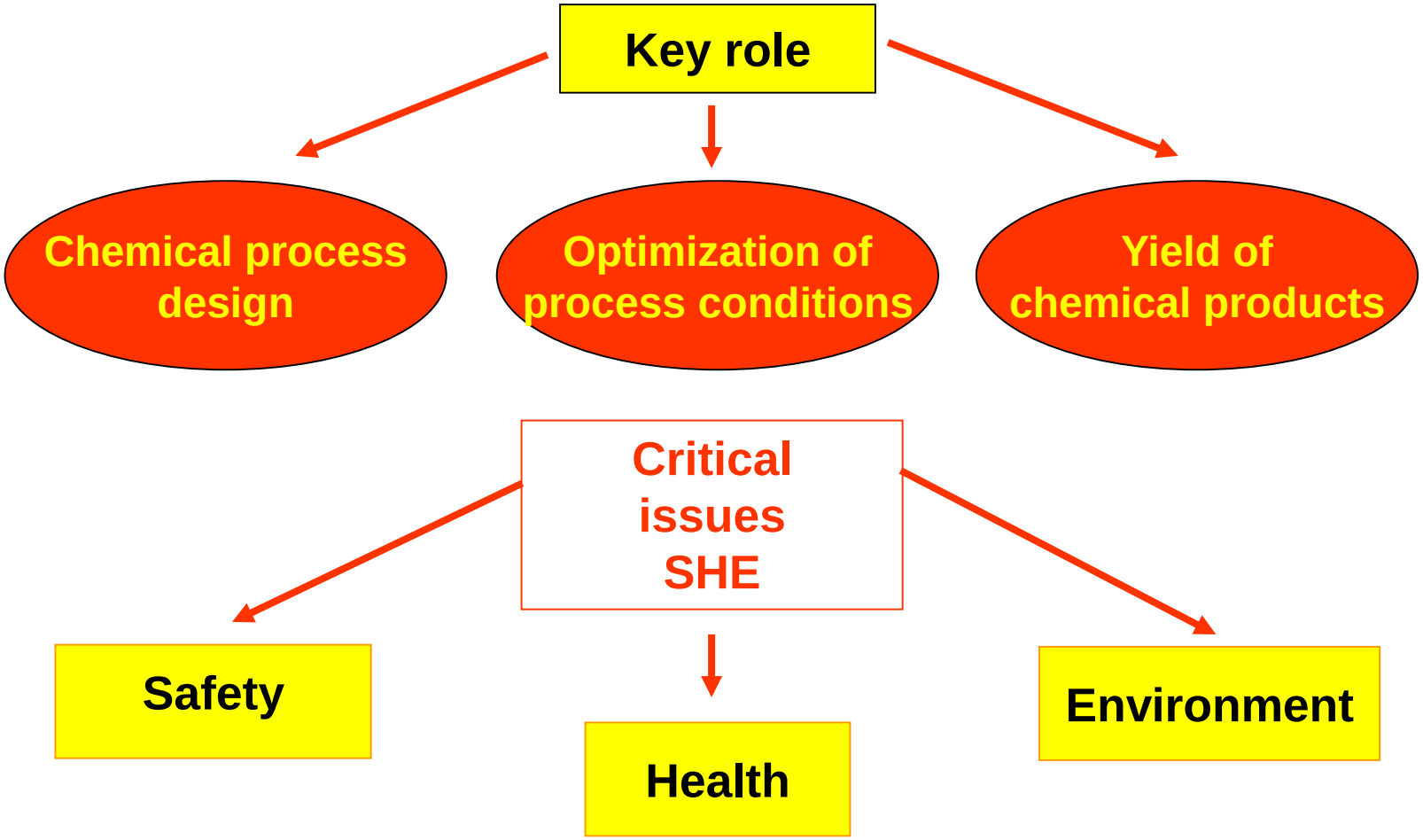
- Significant shift from traditional intensive capital base chemicals
- Stronger emphasis on specialty materials at high added value
- Critical importance of a development of more sustainable chemical process
- Growing of concepts of engineered product in the frame of chemical engineering practice
- Green Engineering



Typical Biological (Antibody) Process.

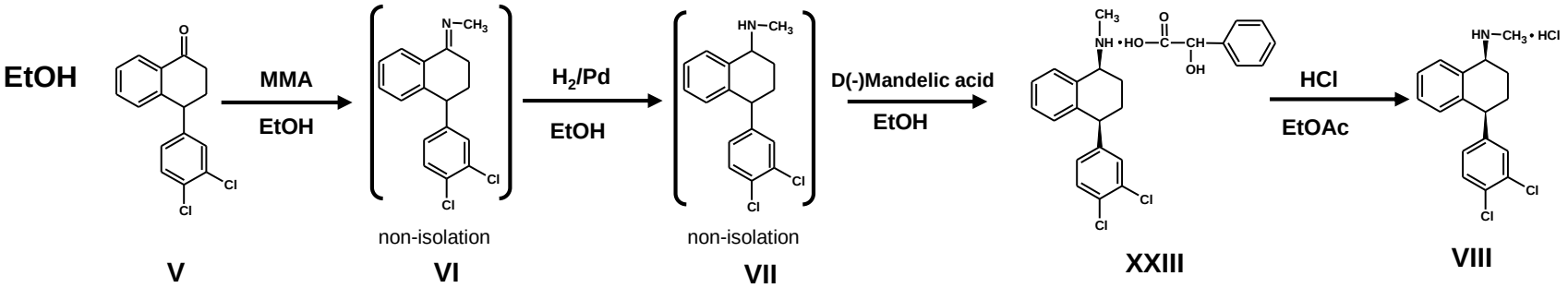


Design in Chemical Engineering.



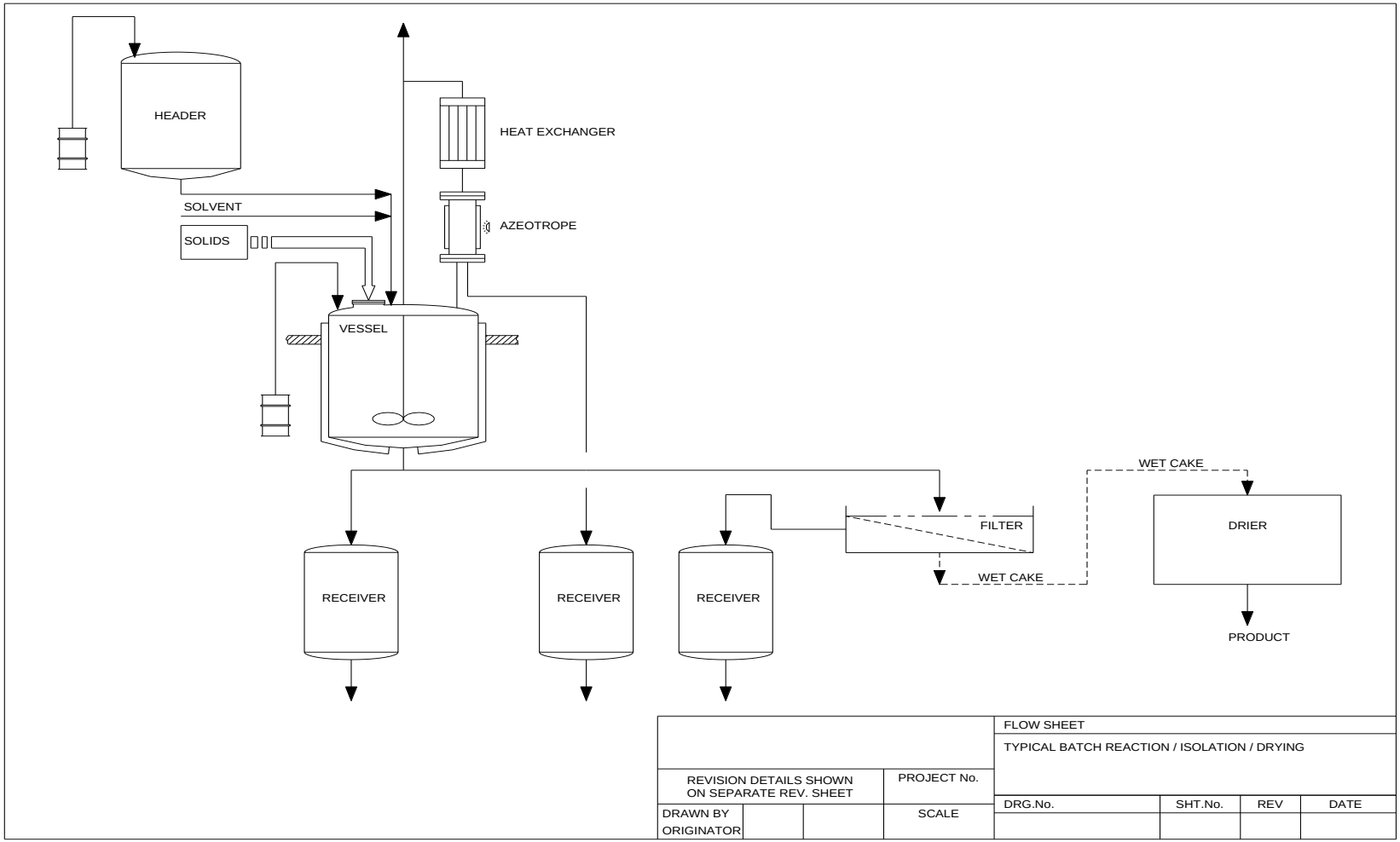
- EXOTIC MATERIALS
- SOPHISTICATED CONTROL
- AIR HANDLING & CONTAINMENT
- CONNECTIVITY & FLEXIBILITY
- MULTI - FUNCTIONALITY

COST ESCALATORS

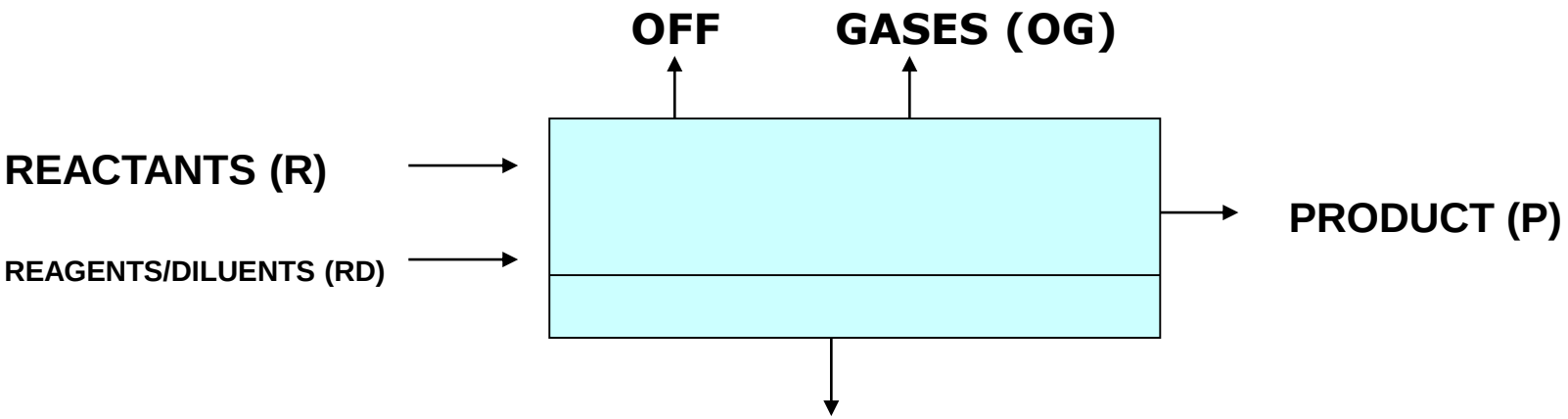


zoloft® (sertraline HCl)

Typical Flow Chart.



Batch Technology.

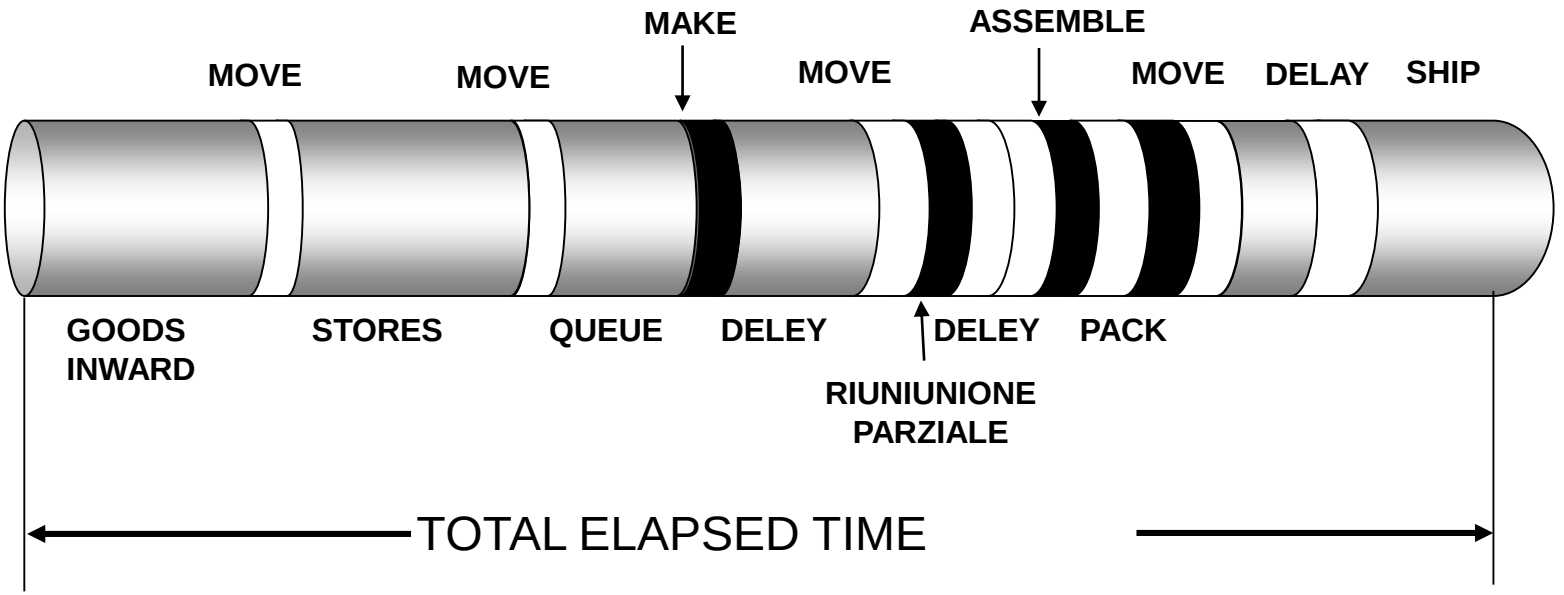


$$\frac{P}{RD + R} \sim 1\%$$

1. OPTIMISE FOR TOTAL MASS BALANCE – NOT KEY REACTANT
2. CHANGE IMPROVE REACTOR DESIGN – SELECTIVITY/RATE/YIELD
   SEPARATION, ANALYSIS

I.E. SWEAT THE PROCESS

Lead Times.



VELOCITY RATIO = SPEED AT WHICH MATERIAL MOVES

$$VR = \frac{\text{SUM OF VALUE ADDS}}{\text{TOTAL ELAPSED TIME}}$$

~ 1%

Potential Ways Forward.

UNIT OPERATIONS APPROACH:

- **REACTOR DESIGN - MUCH MORE INTENSIVE (*Heat & Mass Transfer Controlled*)**
- **PRODUCTS DESIGN - Regio- and Stereo-specificity to improve**
  - Manage morphology
- **PURIFICATION - Speed & precision**
- **SEPARATION - Speed & precision**

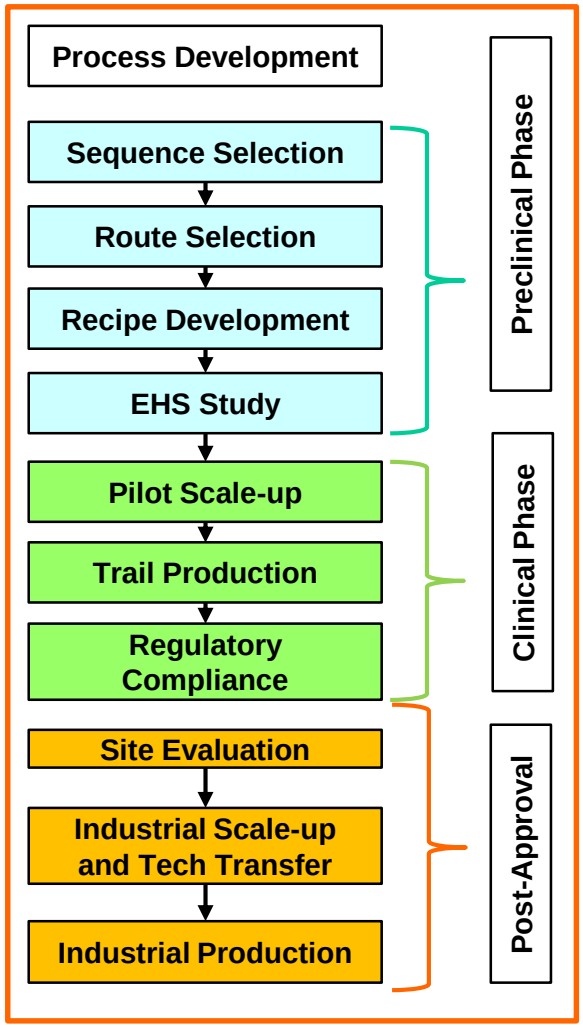
SYSTEM INTEGRATION:

- **Synchronise Unit Operation System**
- **Optimise Process for Minimum Total Mass Balance, not Maximise Yield of Key Reactant.**

How to Improve.

- PROCESS INTENSIFICATION/CATALYSTS
- COST ENGINEERING
- UNIT OP DRIVEN, NOT UNIT PROCESS
- STANDARDISATION/PLUG IN – PLUG OUT
- HIGHER VELOCITY
- HIGHER PRODUCTIVITY
- LOWER CAPEX INTENSITY

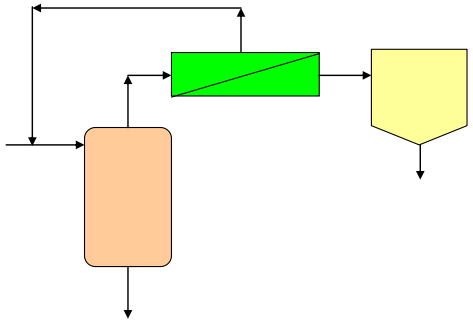
MULTI DISCIPLINARY COLLISIONS



Green Engineering Opportunities.

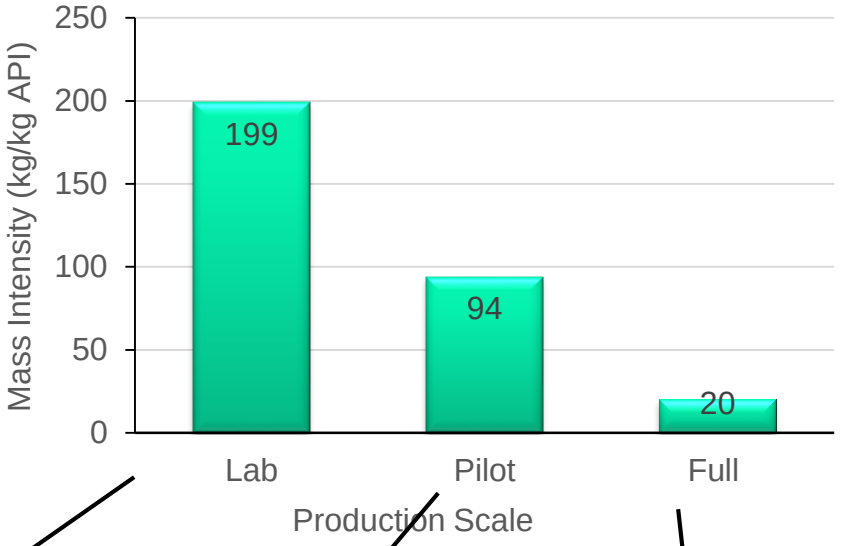
- Investigate process early in development
- Solvent substitution – more benign solvents
- Solvent reduction
- Novel processes for material reuse/recovery
- Reduction in process steps
  - ✓ “Telescoping” to eliminate intermediate isolations

➢ Challenge - maintain drug purity and yield.



Green Engineering Needs.

- Metrics to measure and quantify improvements
  - What to measure, how to quantify – *more than just amount reduced*
- Materials
  - Mass intensity – amount of raw material needed to produce 1 kg of API
  - Solvent intensity
  - Waste intensity
  - Water intensity
- Emissions
- Efficiency
- Energy
- Quantify broader environmental impact.

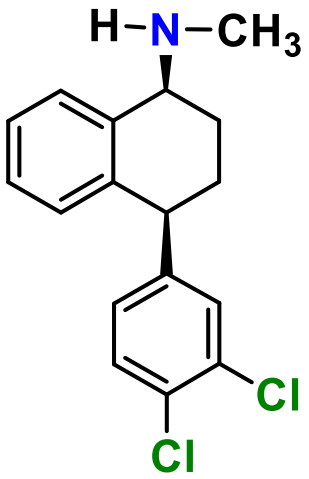


Example: Redesign Sertraline Process.

Sertraline: active component in Zoloft

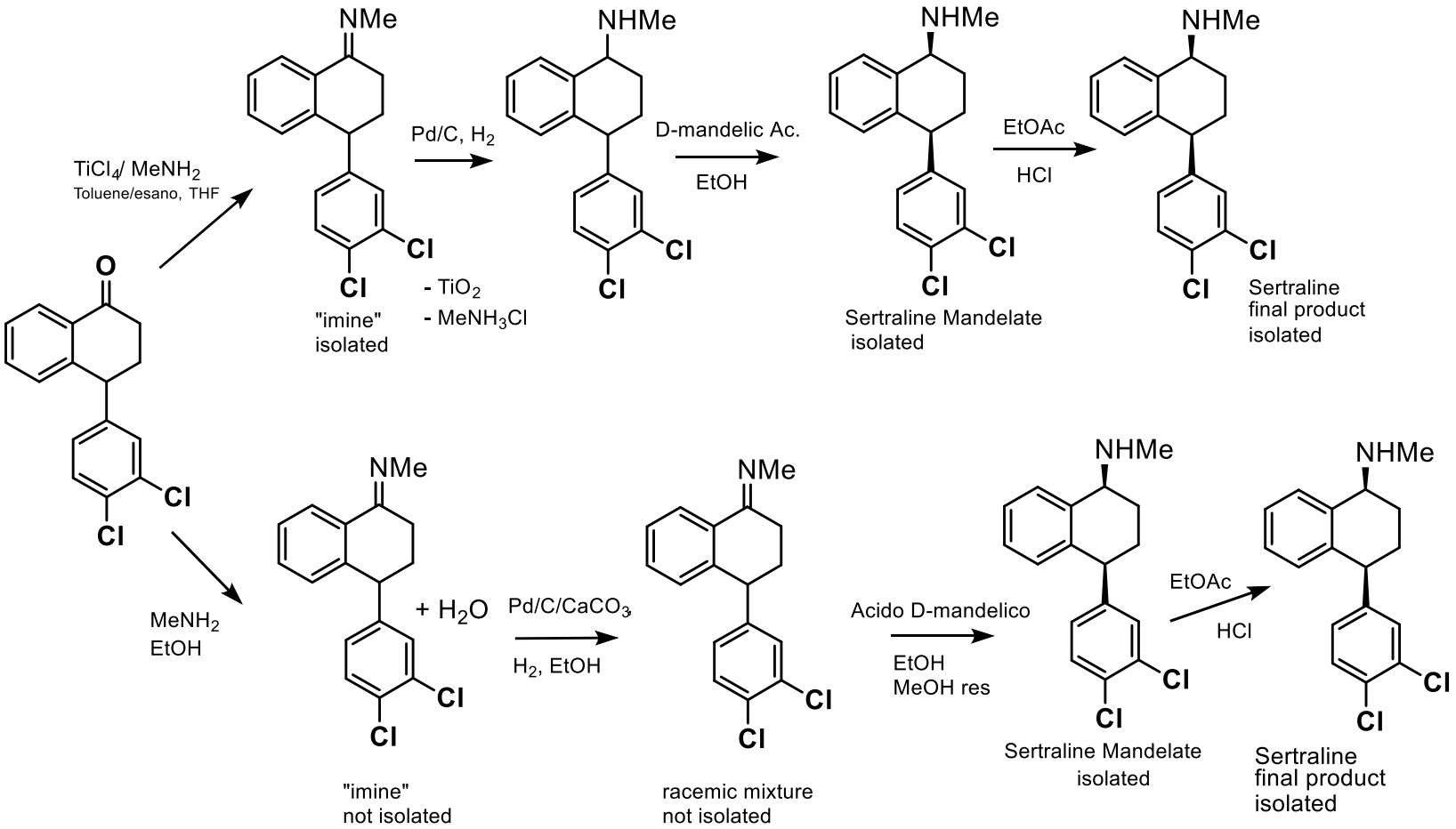
Combined process:

- Doubling up the yield
- Substitution of CH_2Cl_2, THF, toluene and hexane with Ethanol
- Elimination of 140 ton/year of $TiCl_4$ use
- Elimination of 150 ton/year of 35% HCl

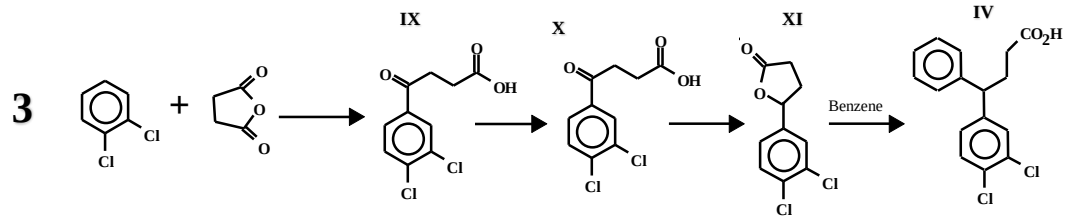


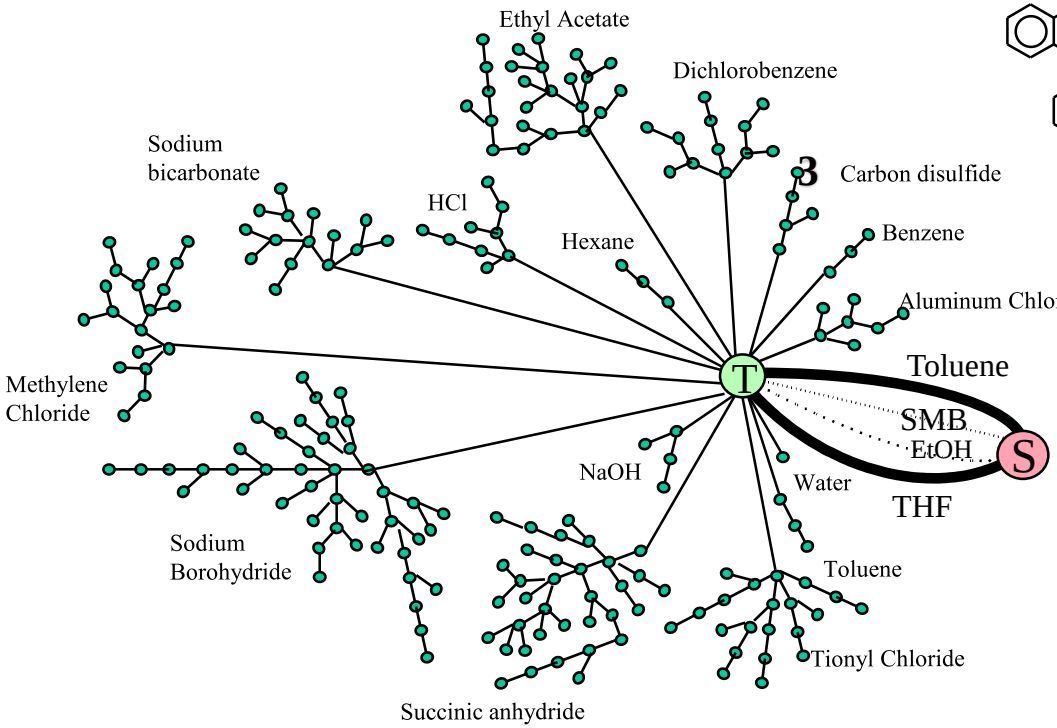
Pfizer

Redesign Sertraline Process.



Efficiency of “Carbon Frame” in the Sertraline Synthesis.





Improvement of 10% in the Efficiency of Carbon Use.

- Inside the Company (kg/kg Sertraline):

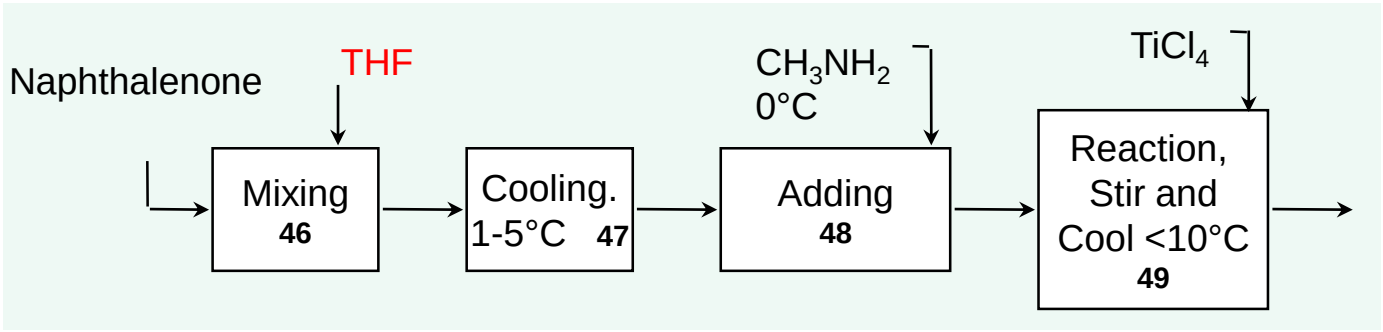
97 ⇒ 96 ⟷ 1 (*most wastes are solvents*)

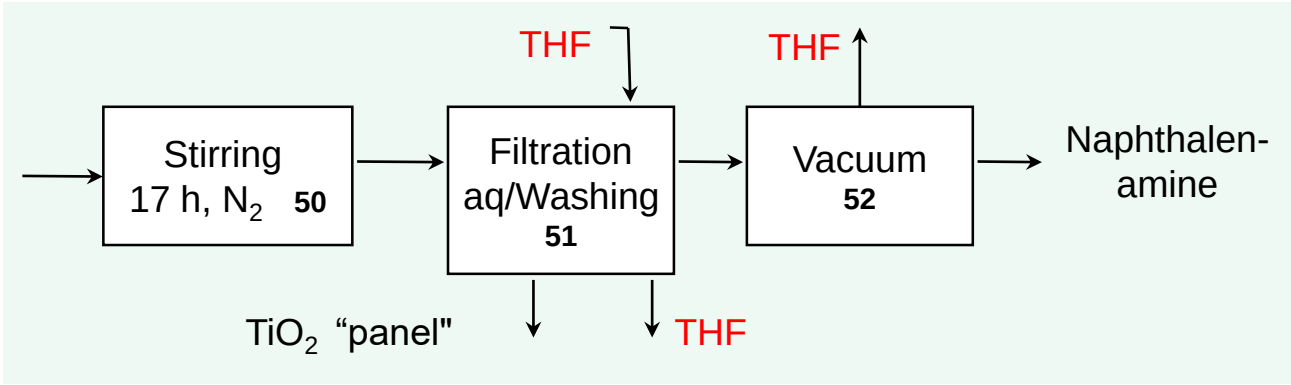
- In overall Pharma Complex (kg/kg Sertraline)

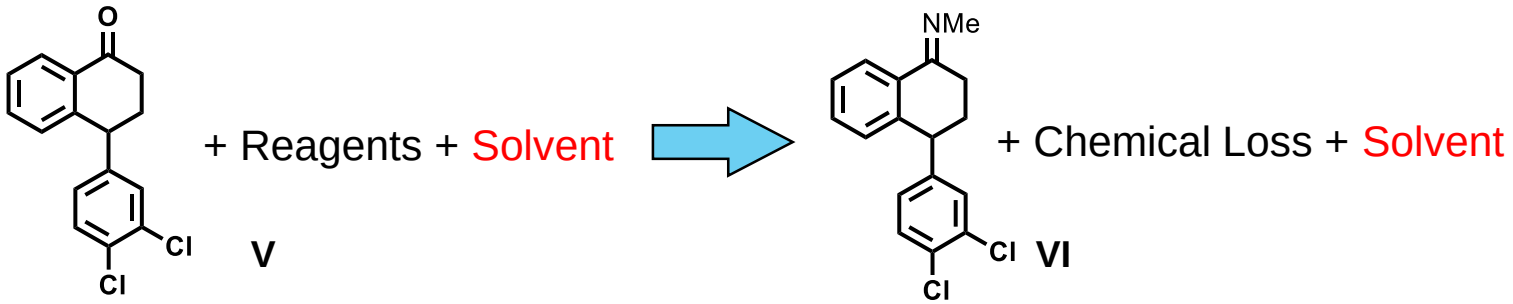
39,098 ⇒ 35,794 ⟷ 3,304

Impact more 3,000-times higher!

Efficiency in the Use of Solvents (V → VI).

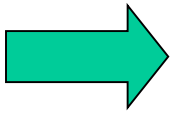




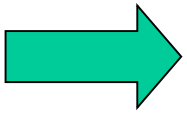


Improvement of 10% in the Use of Solvents.

- Inside the Company (kg.kg Sertraline)

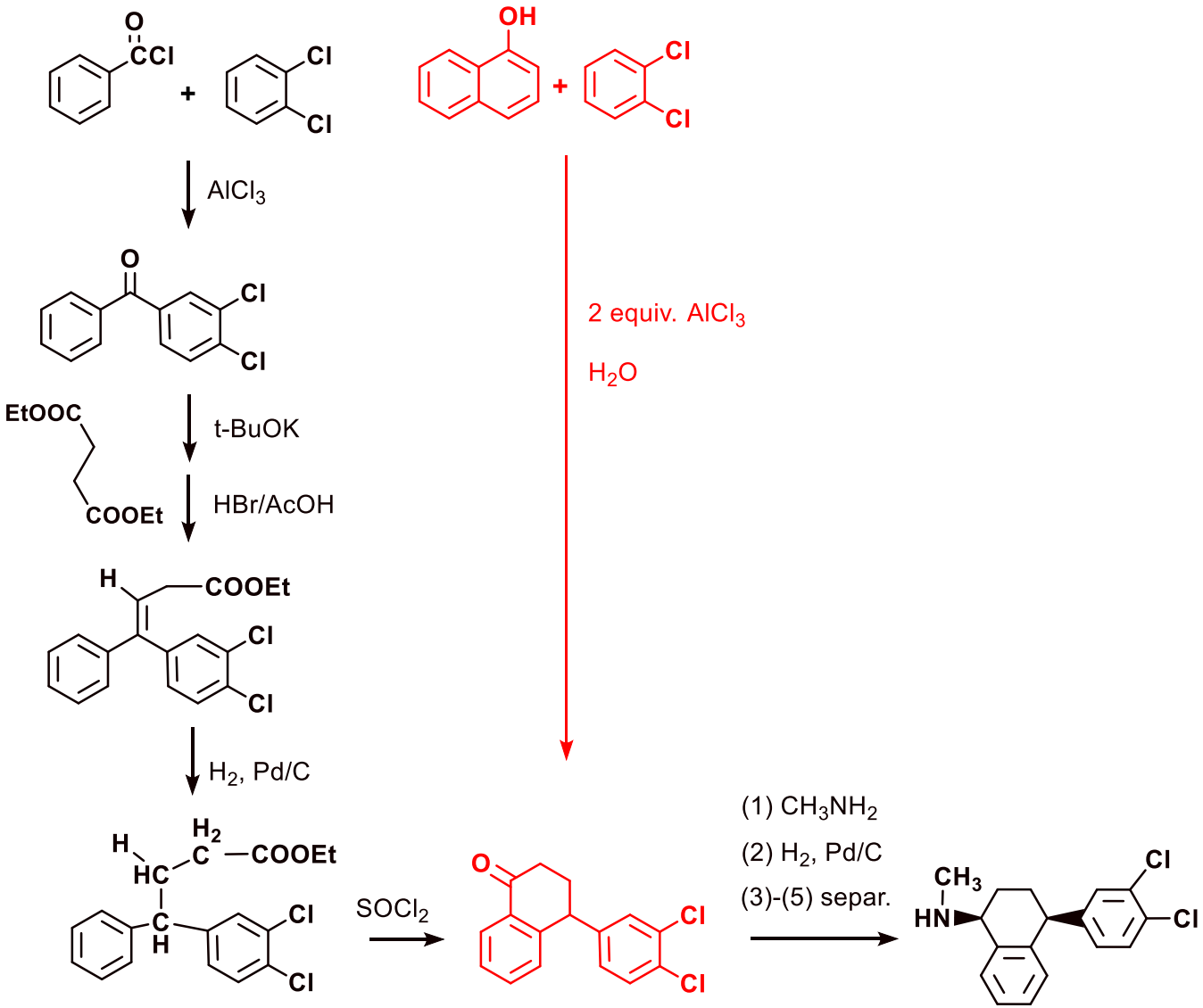
97  89 ⟷ 8

- Inside the Pharma Complex (kg/kg Sertraline)

39,098  38,493 ⟷ 605

The effect is higher inside the Society, but higher impact is out of Society.

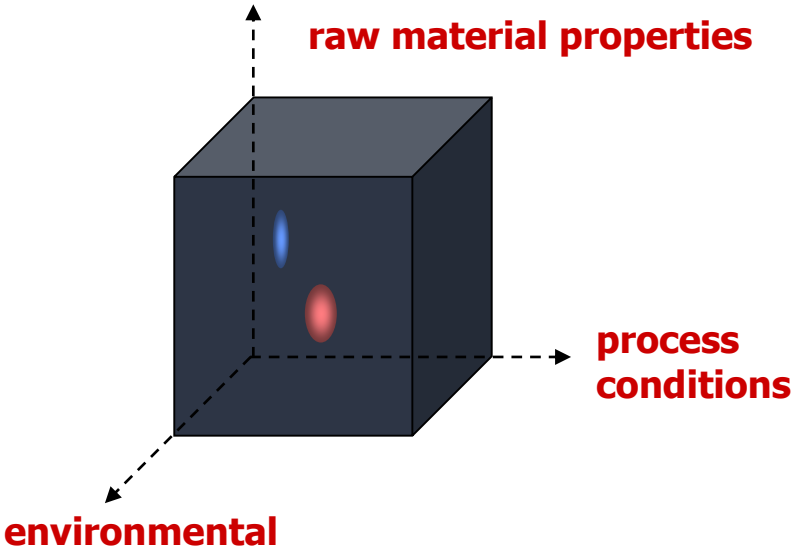
Redesign of Sertraline Process.



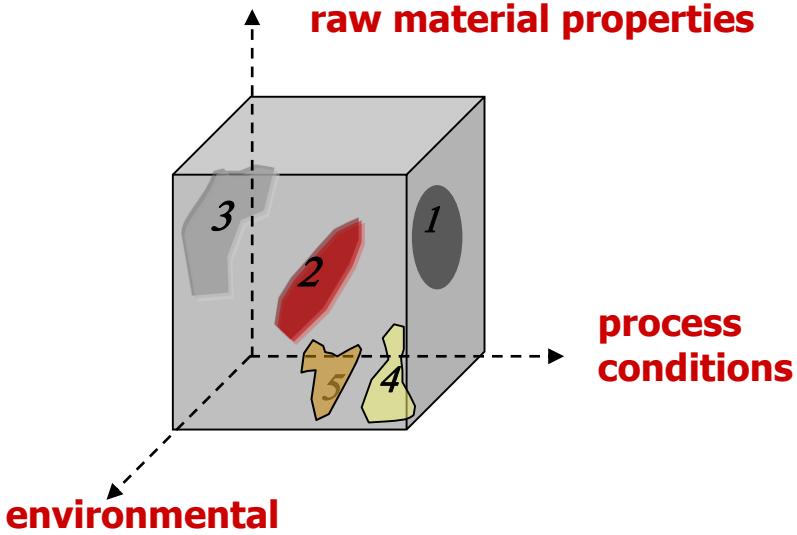
Pharmaceutical Process Development: Optimization.

- Optimization Studies
  - Find regions of process parameters where performance is most stable
  - Design process to operate within this region (PAT).

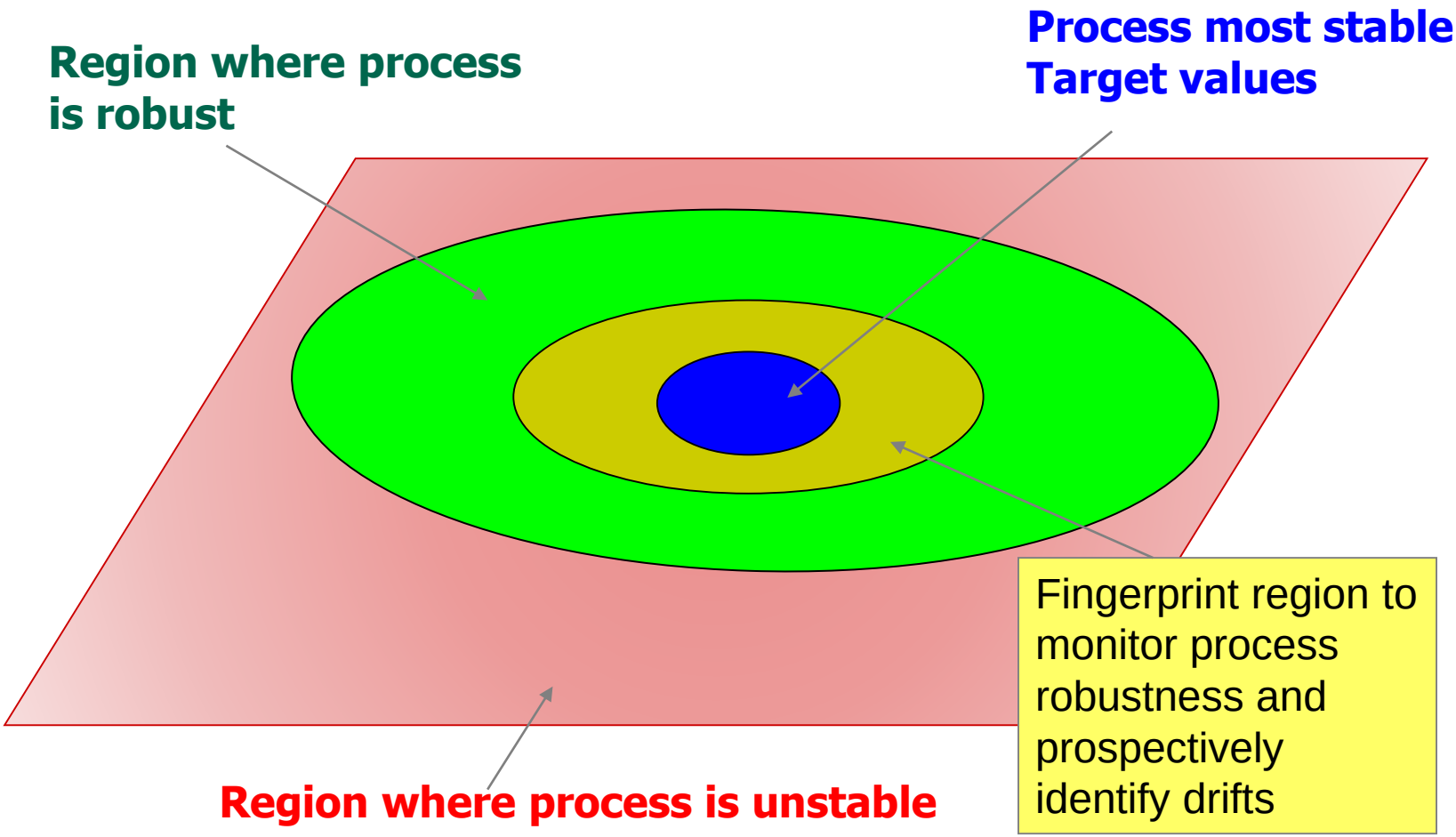
The current norm



The future

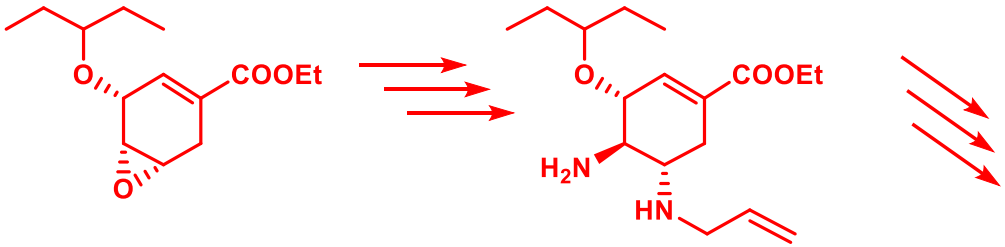


Process Optimization via PAT.

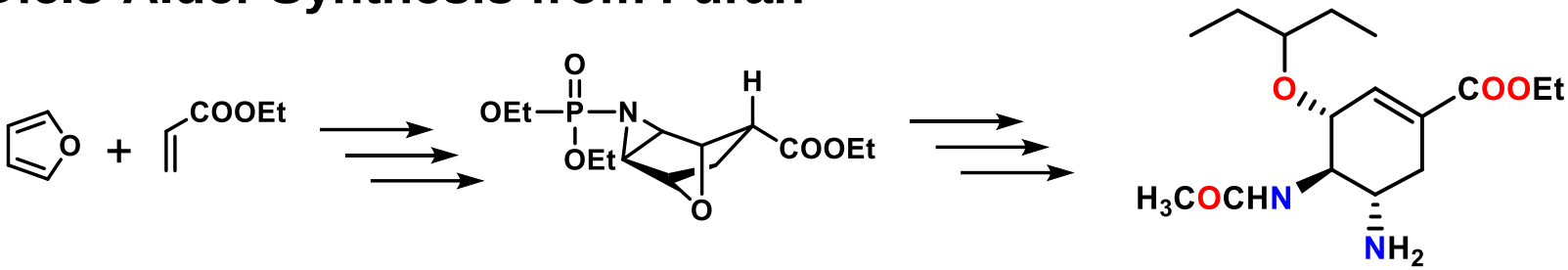


Alternative for Tamiflu™ (Oseltamivir Phosphate).

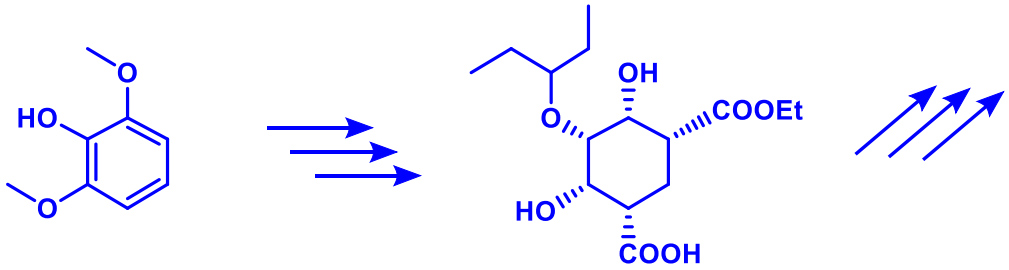
- **Synthesis of allyl amine without Azide**



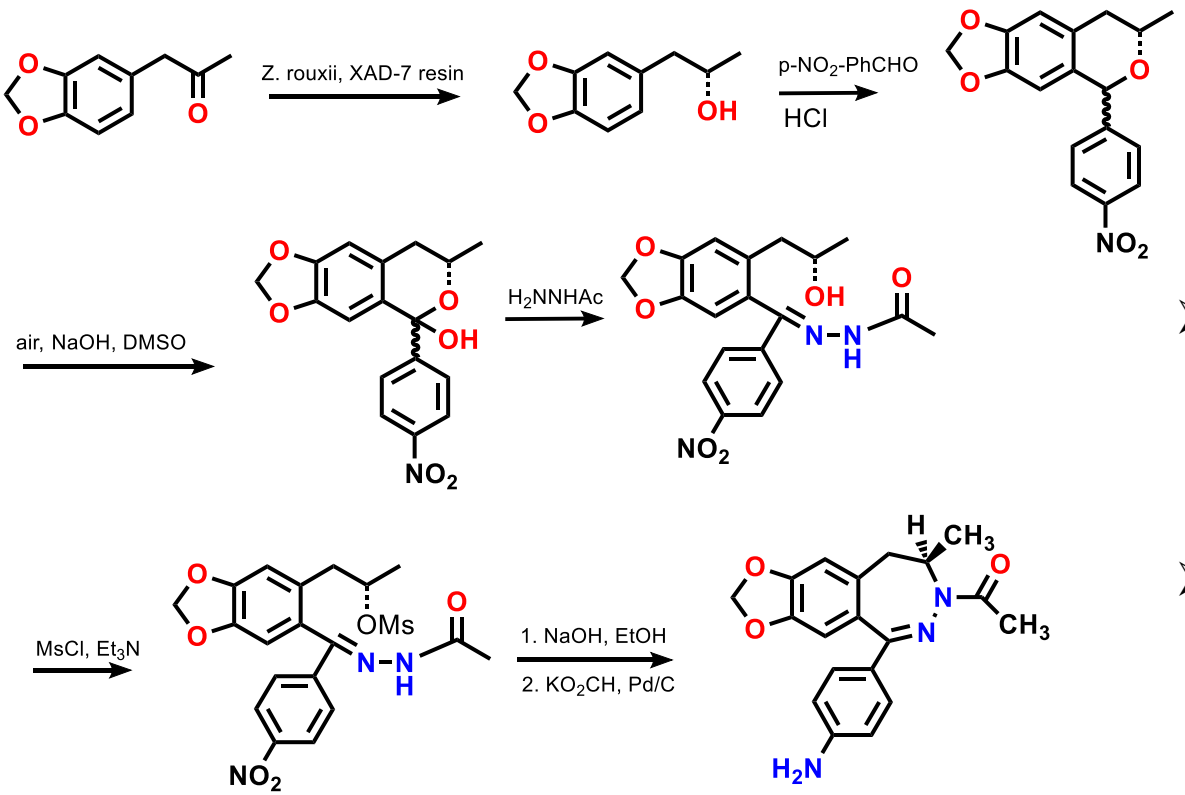
- **Diels-Alder Synthesis from Furan**



- **Elaboration of Aromatic ring: meso approach**



Redesign of a NCS Compound: Benzodiazepine Synthesis.



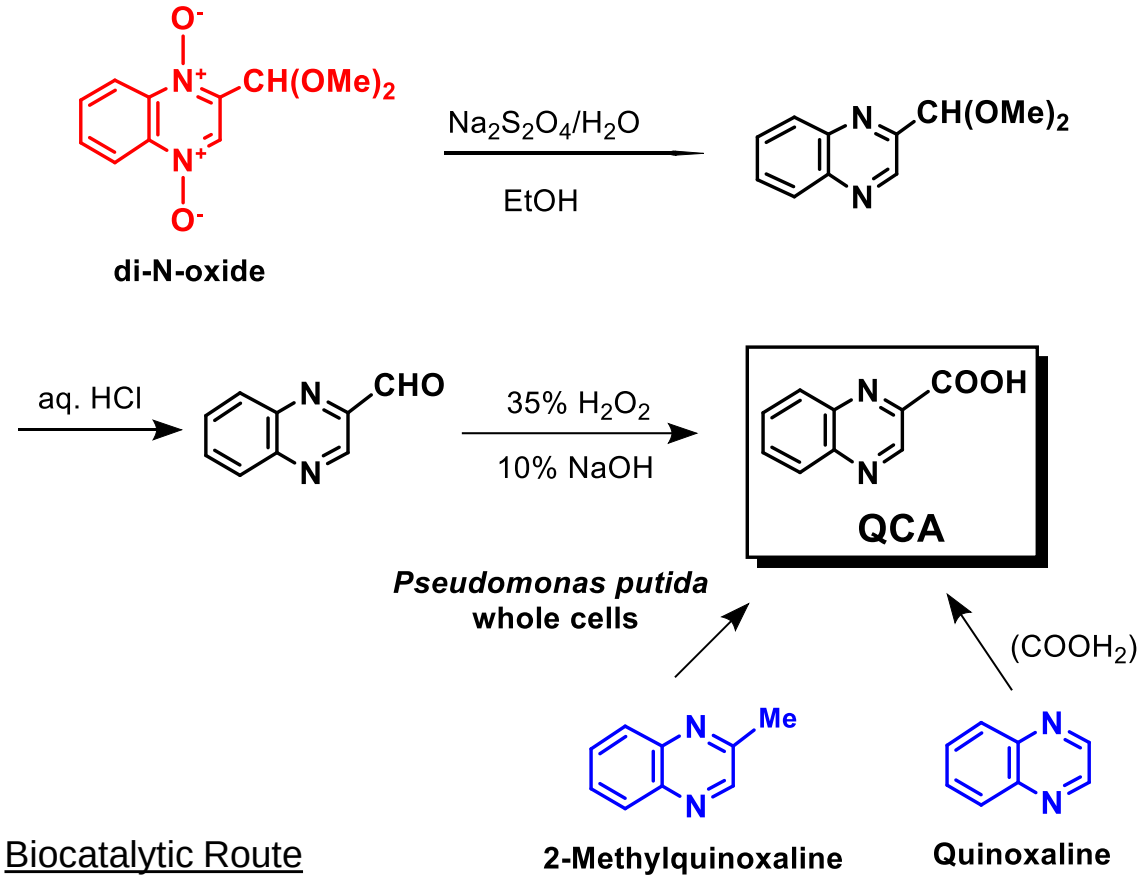
- Improved synthesis of an active drug for nervous central system.
- Interdisciplinary approach, which combine chemistry, microbiology and engineering.

For each 100 kg of product were eliminated:

- 300 kg of chromium wastes
- 34,000 liters of solvents

Eli Lilly and Company

Chemical & Biocatalytic Routes to QCA.



Chemical Route

- 3 steps, 35% yield
- Di-*N*-oxide: mutagenic & high energy intermediate

Biocatalytic Route

- 1 step (3 enzyme reactions), 86% yield
- Aqueous reaction at 28°C

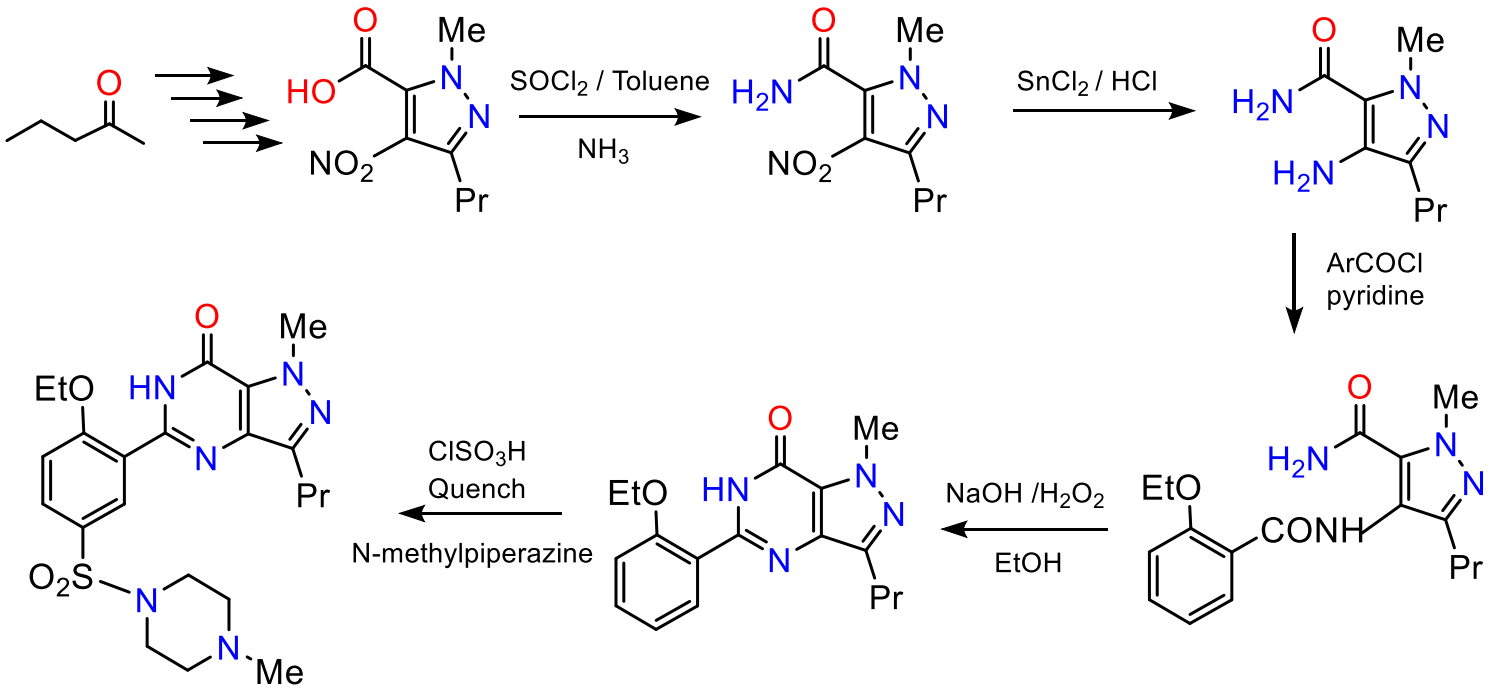
Chemical & Biocatalytic Process Comparison.

Raw materials for 1 kg QCA

Chemical Process			*P. putida* Process	
di-*N*-oxide	3.9 kg		2-methylquinoxaline	0.97 kg
$Na_2S_2O_4$	5.7 kg		benzyl alcohol	2.9 L
35% H_2O_2	6.5 L		*p*-xylene	0.9 L
4N HCl	13.6 L		4N HCl	3.8 L
10% NaOH	11.7 L		10% NaOH	1.7 L
chloroform	142 L		inorganic salts	0.75 kg
N,*N*-dimethylacetamide	36 L		trace elements	0.005 kg
ethanol	18 L		H_2O	79 L

- Biocatalytic route avoids hazardous di-*N*-oxide and uses 4x less starting material
- Reduced organic solvent consumption for biocatalytic route (3.8 L/kg QCA) vs. chemical process (196 L/kg QCA). N.B.: $CHCl_3$ induce cancer.

Sildenafil Route Selection.



Linear Synthesis (no convergency)
Poor from an environmental perspective

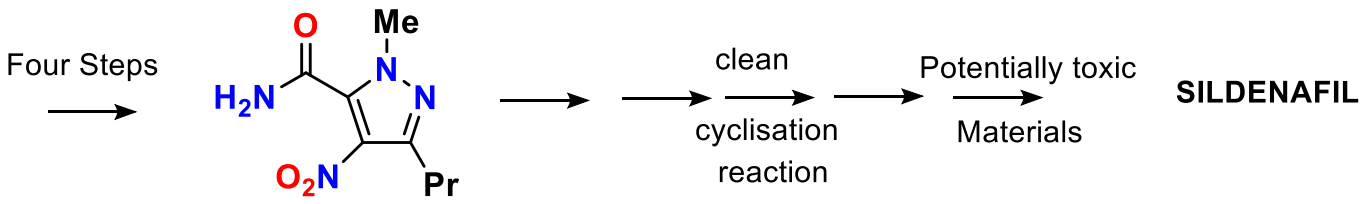
Tin Chloride Reduction Step

Late Stage Chlorosulphonation generates a lot of aqueous waste, difficult to scale-up.

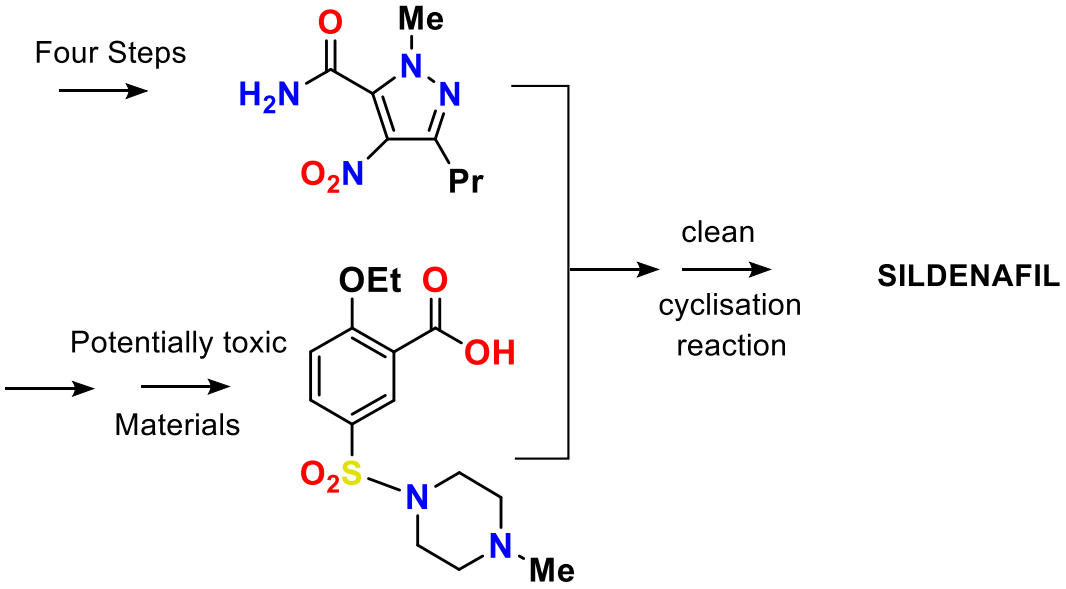
Usual Challenging Solvents (e.g. pyridine)

Pfizer

Sildenafil Route Selection.

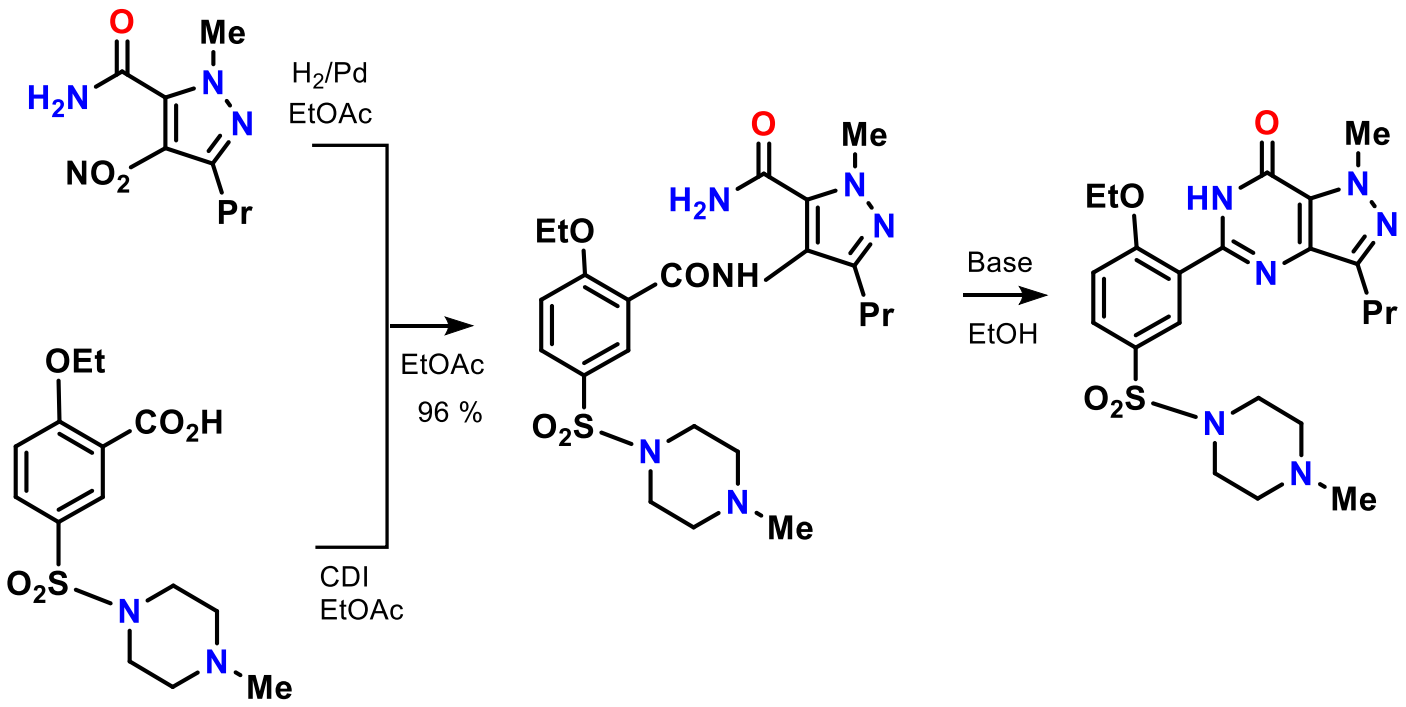


Medicinal Chemistry Route: The clean reaction is in the middle of the synthesis
The potentially toxic materials are in the final step.



Commercial Route: The synthesis was redesigned to introduce convergency
The clean reaction is in the final step.

Late Synthetic Stages.



Use of ethyl acetate in all three reactions, hydrogenation, activation, acylation leads to an easy solvent recovery by distillation and clean environmental profile.

Final step is run very concentrated hence very little organic waste.

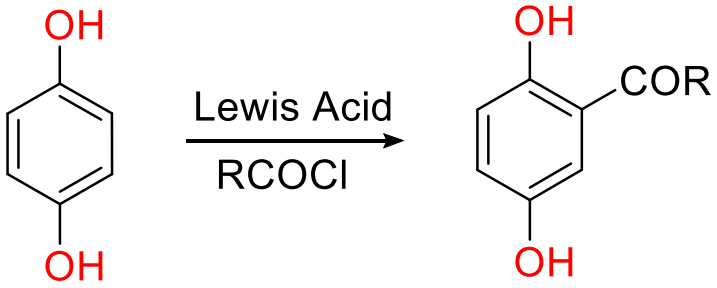
High yields late in the synthesis reduce the environmental impact of early steps

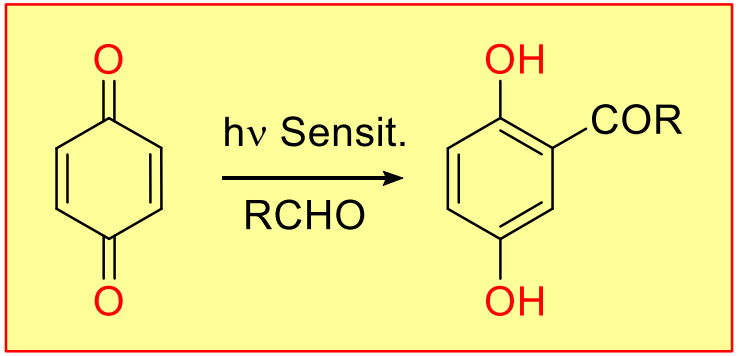
Alternative in Friedel-Craft.

Traditional reagents in Friedel-Crafts reactions:

Lewis Acid: aluminum chloride, tin(IV) chloride, boron trifluoride

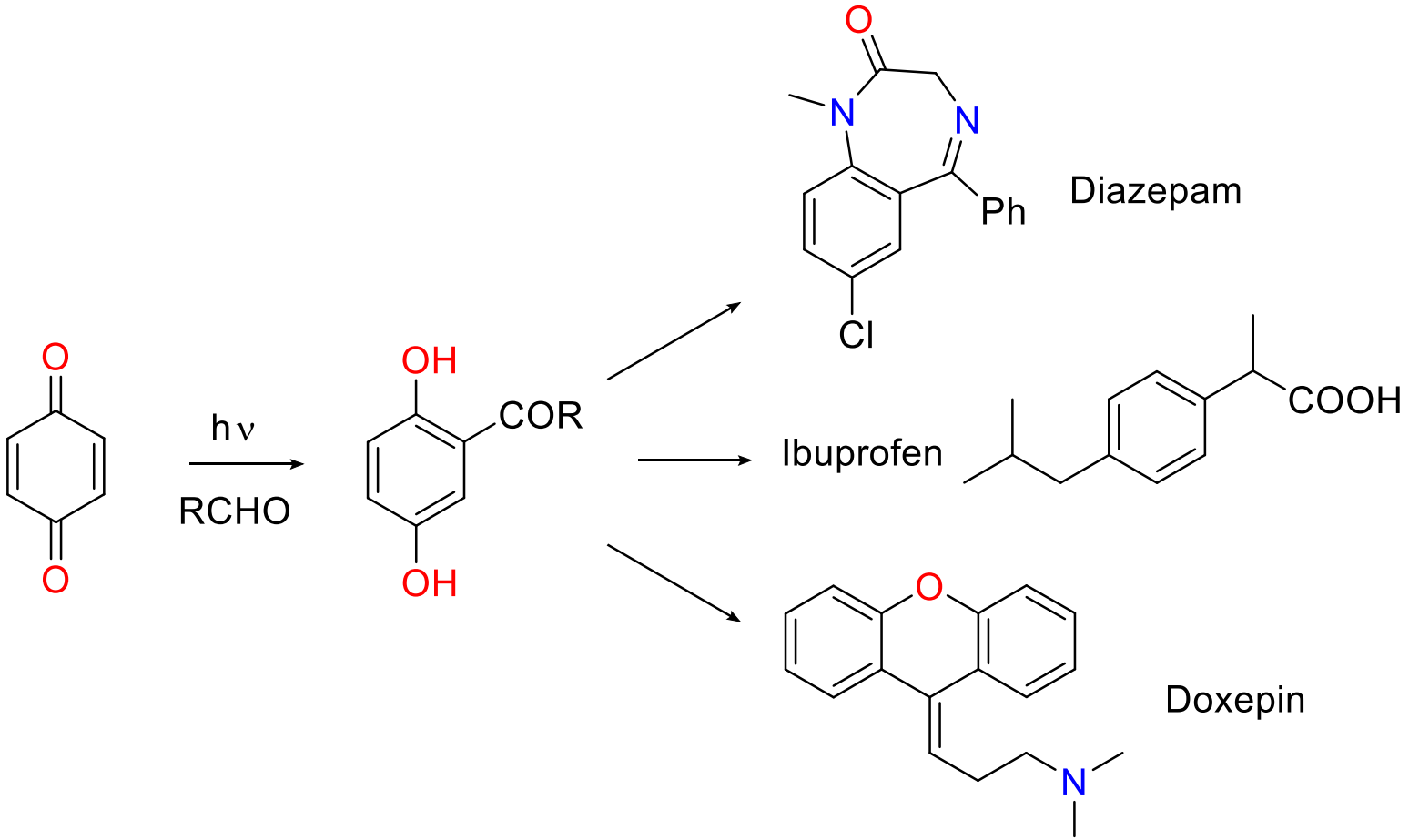
Solvents: aromatic hydrocarbons, nitrobenzene, carbon disulfide, methylene chloride



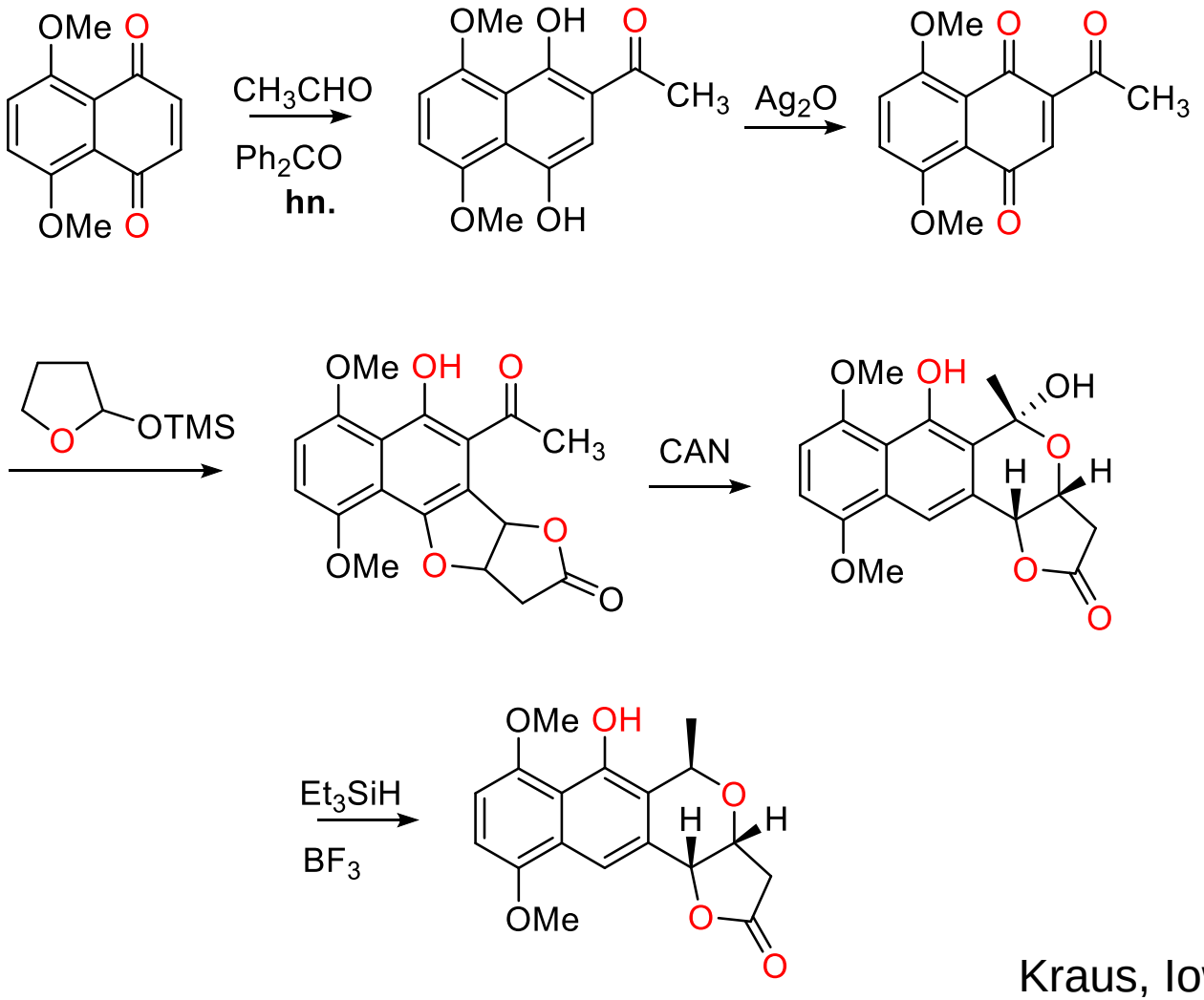


- Photochemical acylation of benzoquinone with benzaldehyde

Photochemical Alternative in Friedel-Crafts.



Other Photochemical Applications.

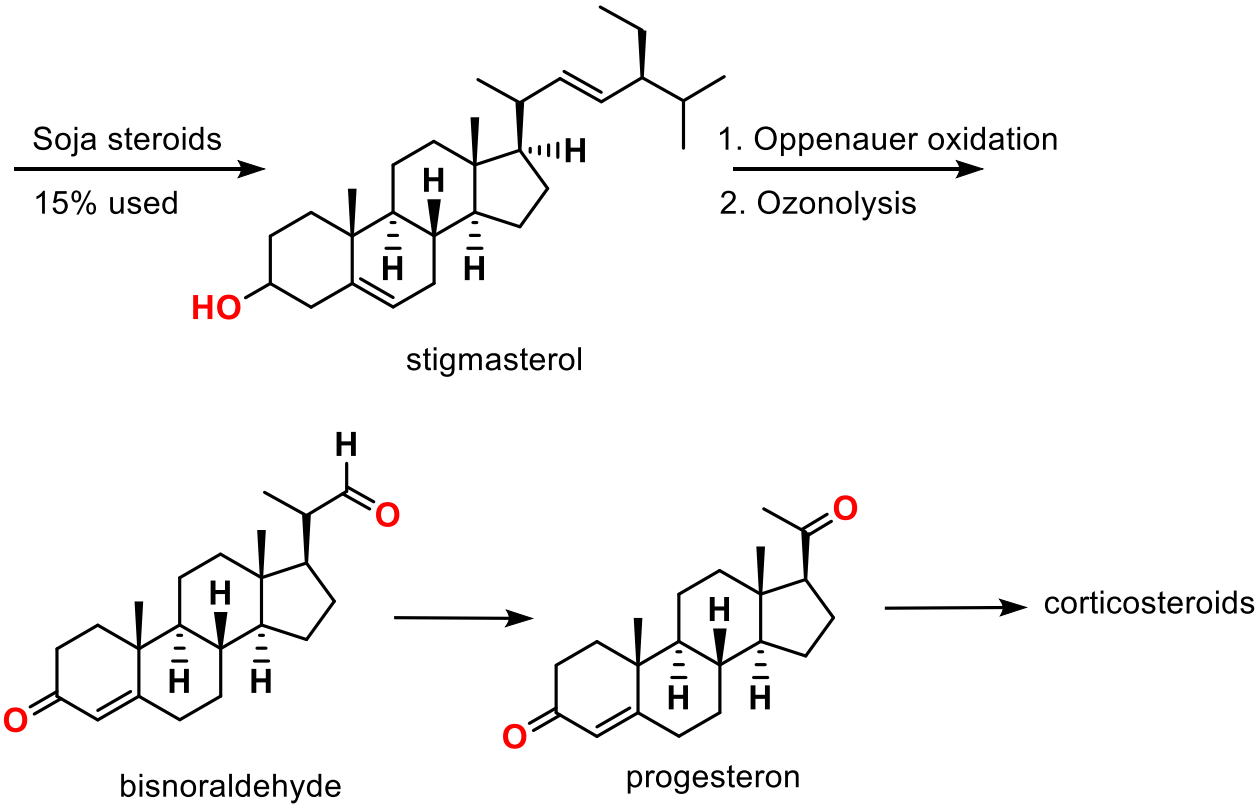


Kraus, Iowa State

Applications in Pharma Field.

Traditional synthesis of Progesterone

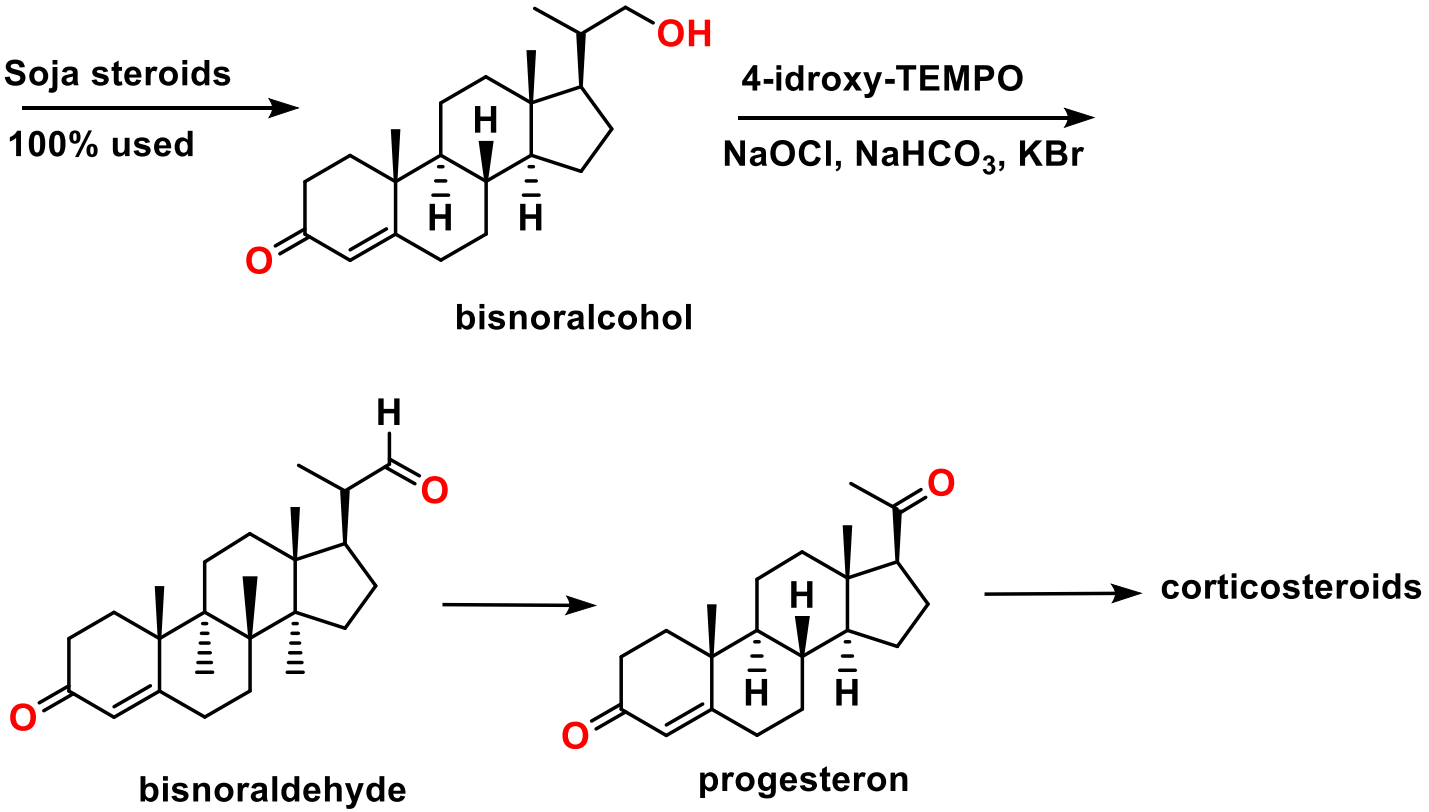
- Great use of EDC, relevant volumes of aqueous and organic wastes



Pharmacia - Upjohn

Alternative Synthesis of Progesterone.

- 89% less organic not recovered wastes,
- 79% less aqueous wastes



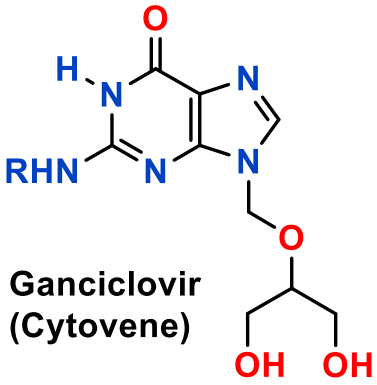
Pharma Applications.

Cytovene

- antiviral agent used in treatment of retinitis infections by cytomegalovirus (CMV)
- Patients with Aids and with transplant of solid tissues

Improved synthesis:

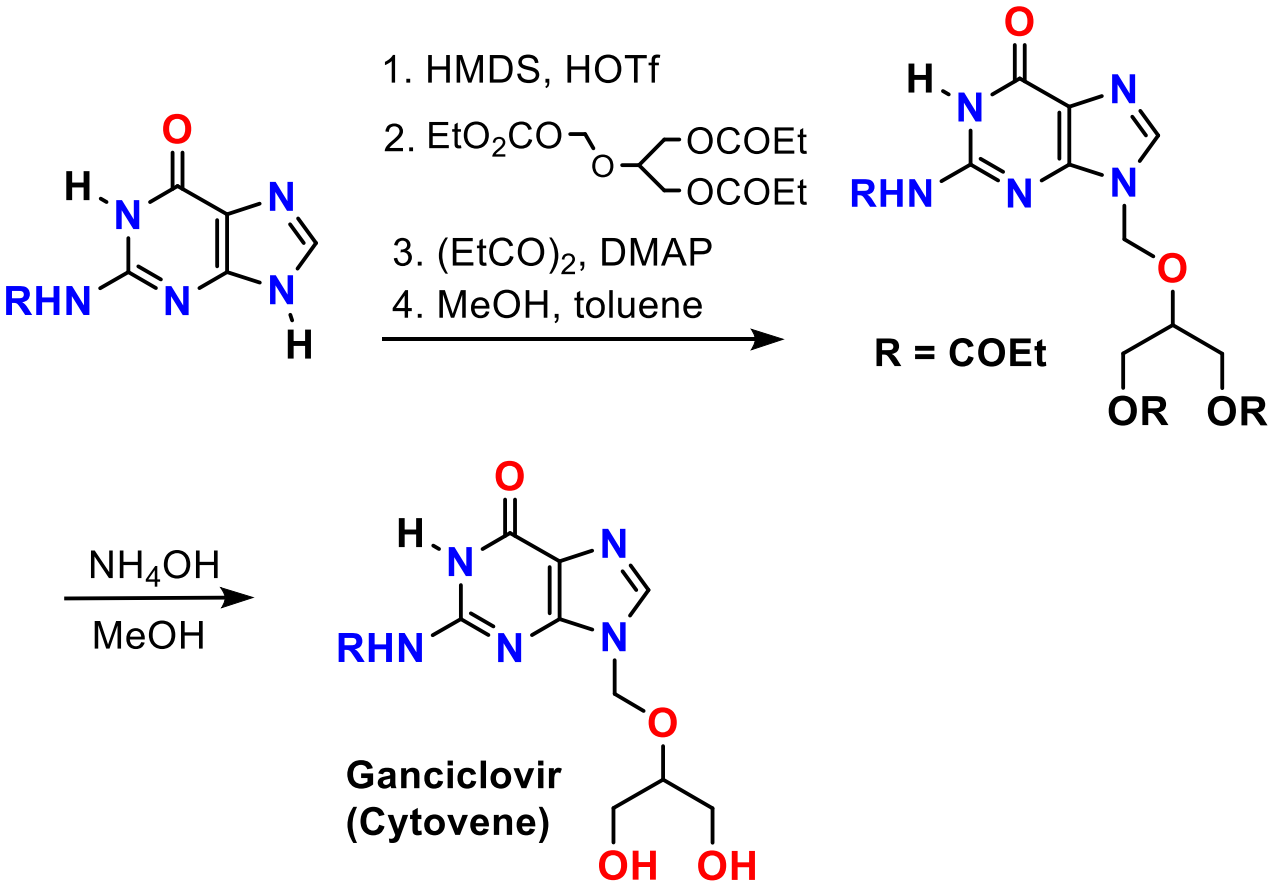
- reduced chemical process stages from 6 to 2
- reduced the number of reagents and intermediates from 22 to 11
- eliminated 1.12 millions kg/year of liquid wastes
- eliminated 25,300 kg/year of solid wastes
- overall increase of yield: 25%



Ganciclovir
(Cytovene)

Pharma Applications (2).

GTE Process – Cytovene Synthesis

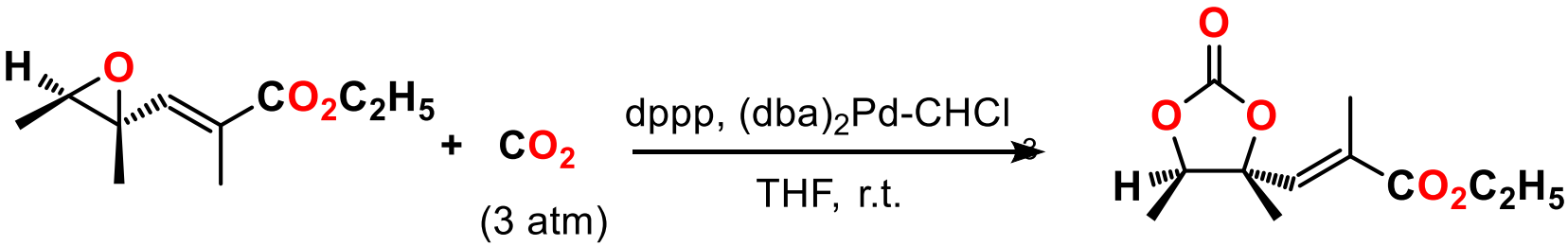


Roche Colorado Corp.

Pharma Applications (3).

(+)-Citreoviridin Synthesis

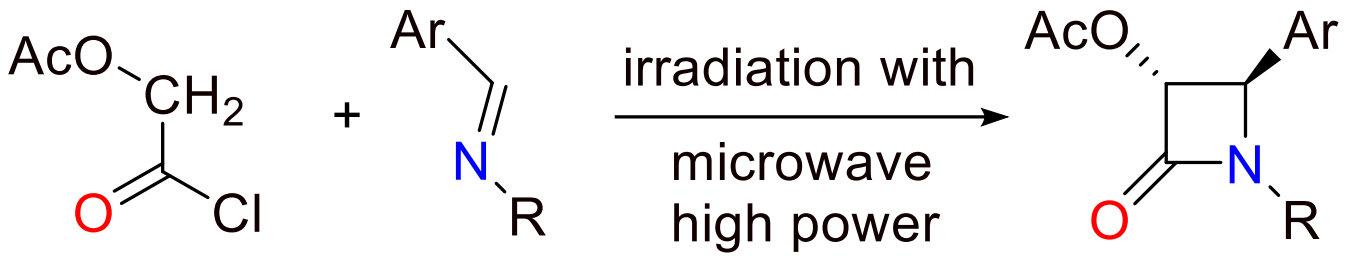
- ATP synthase inhibitor



Trost, Stanford University

Pharma Applications(4).

Trans-β-lactams synthesis through microwave induced organic reactions (intermediate in the synthesis of Taxol/Taxotere)

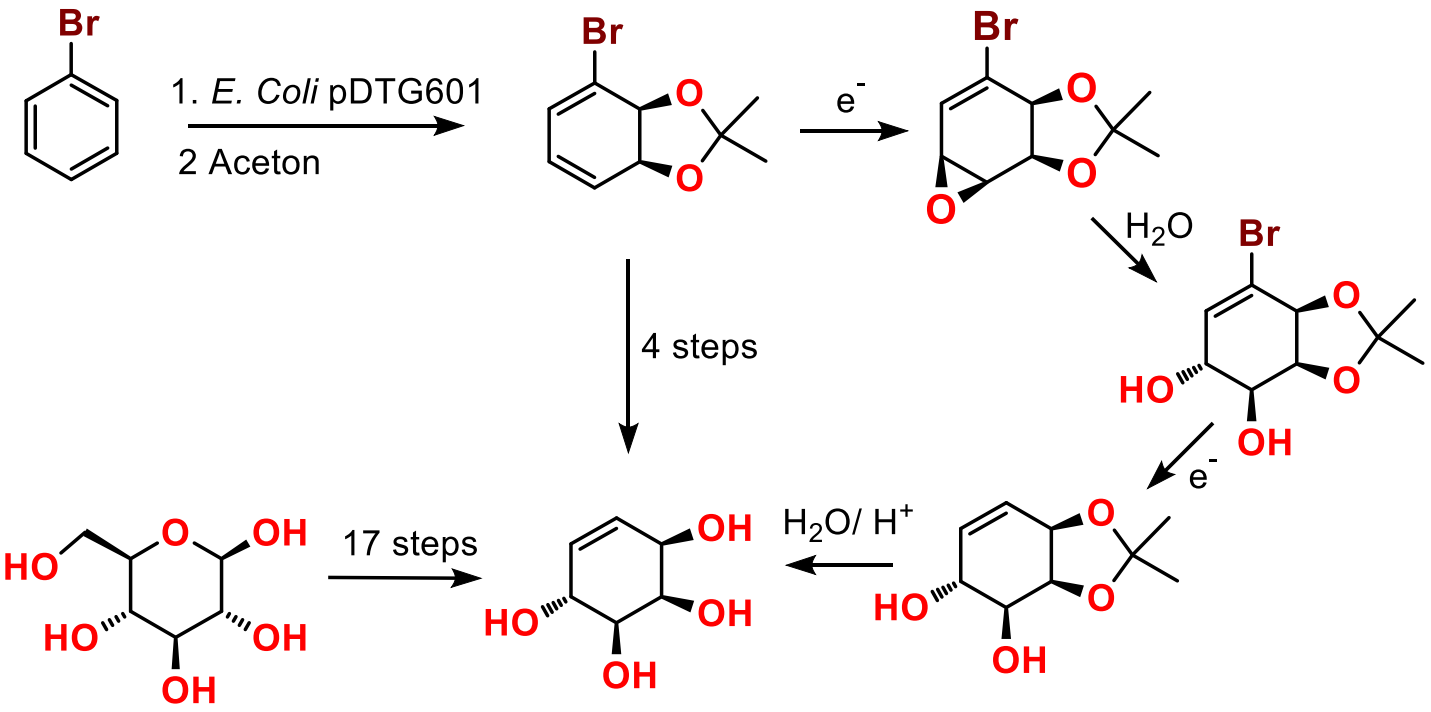


Bose, Stevens Institute of Technology

Applications via Combined Methodologies.

Tandem synthetic methods assisted by enzymes and electrochemistry

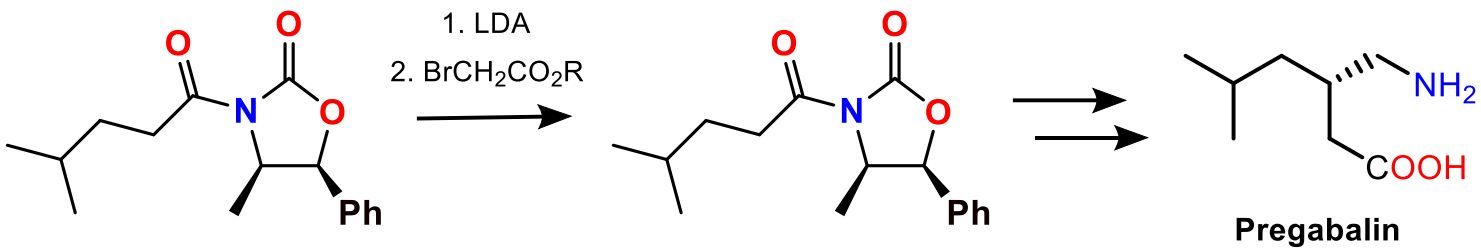
Conduritol C Synthesis:



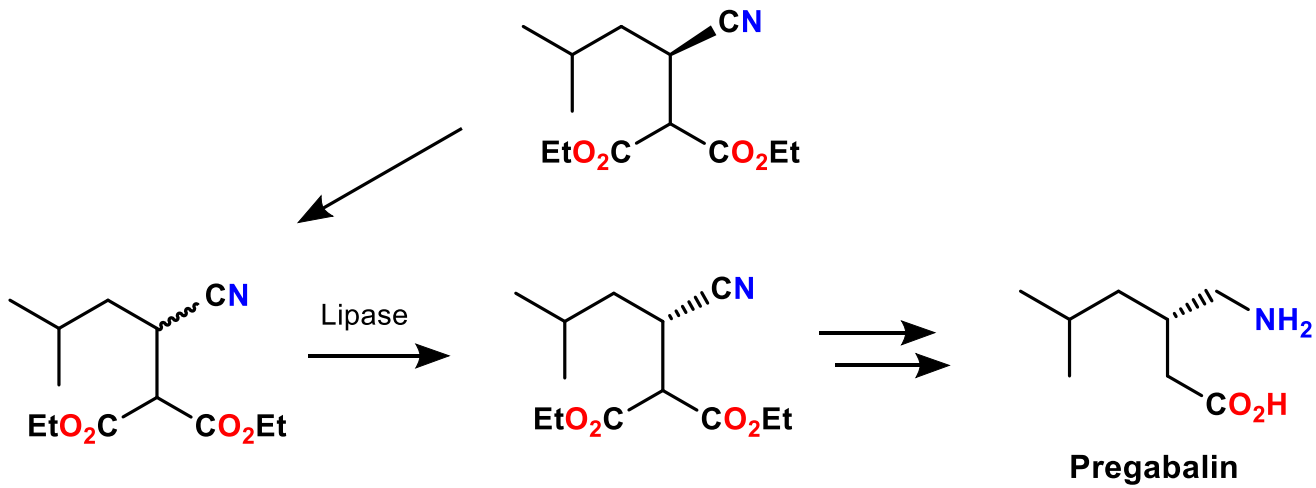
(Hudlicky, University of Florida)

Enzyme Use for Chiral Compounds: Synthesis of Pregabalin.

Research-scale synthesis

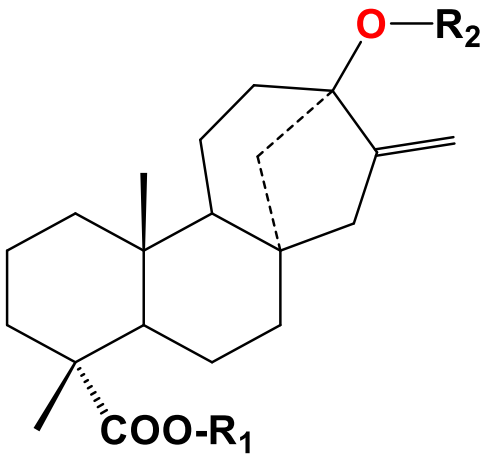


Final manufacture-scale synthesis



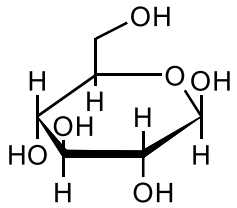
The savings come about because efficient syntheses that avoid exotic reagents, minimize energy use and replace organic solvents with water are invariably cheaper to perform.

Stevia Sweeteners.

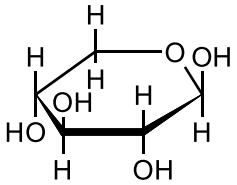


Name	R1	R2
Stevioside	Glcβ1-	Glcβ1-2 Glcβ1-
Rebaudioside A	Glcβ1-	Glcβ1-2(Glcβ1-3)Glcβ1-
Rebaudioside B	H-	Glcβ1-2(Glcβ1-3)Glcβ1-
Rebaudioside C	Glcβ1-	Rhaα1-2(Glcβ1-3)Glcβ1-
Rebaudioside D	Glcβ1-2Glcβ1-	Glcβ1-2(Glcβ1-3)Glcβ1-
Rebaudioside E	Glcβ1-2Glcβ1-	Glcβ1-2Glcβ1-
Rebaudioside F	Glcβ1-	Xylβ1-2(Glcβ1-3)Glcβ1
Dulcoside A	Glcβ1	Rhaα1-2Glcβ1-
Rubusoside	Glcβ1-	Glcβ1-
Steviolbioside	H-	Glcβ1-2Glcβ1-

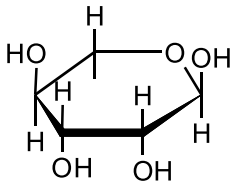
Glc, Rha and Xyl represent, respectively, glucose, rhamnose and xylose sugar moieties.



β-D-Glucopyranose

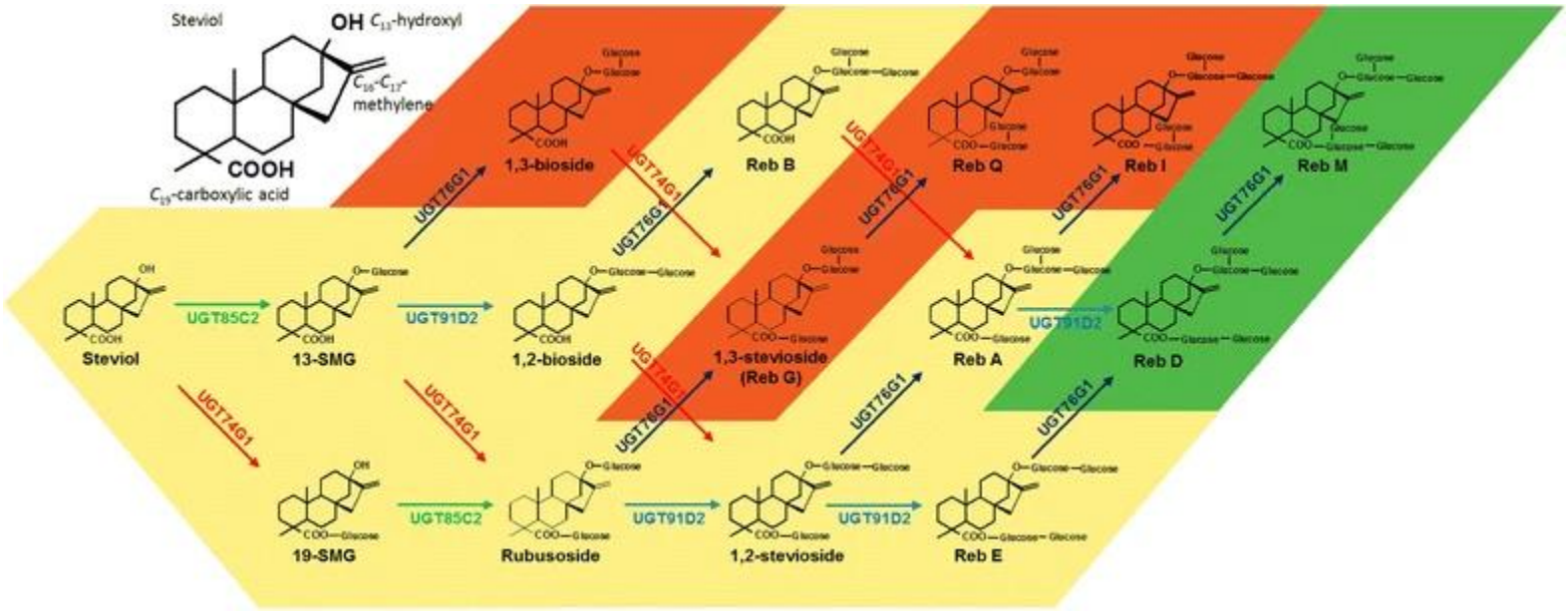


β-D-Xylopyranose



β-D-Rhamnopyranose

Stevia Derivatives Selection for Sweeteners

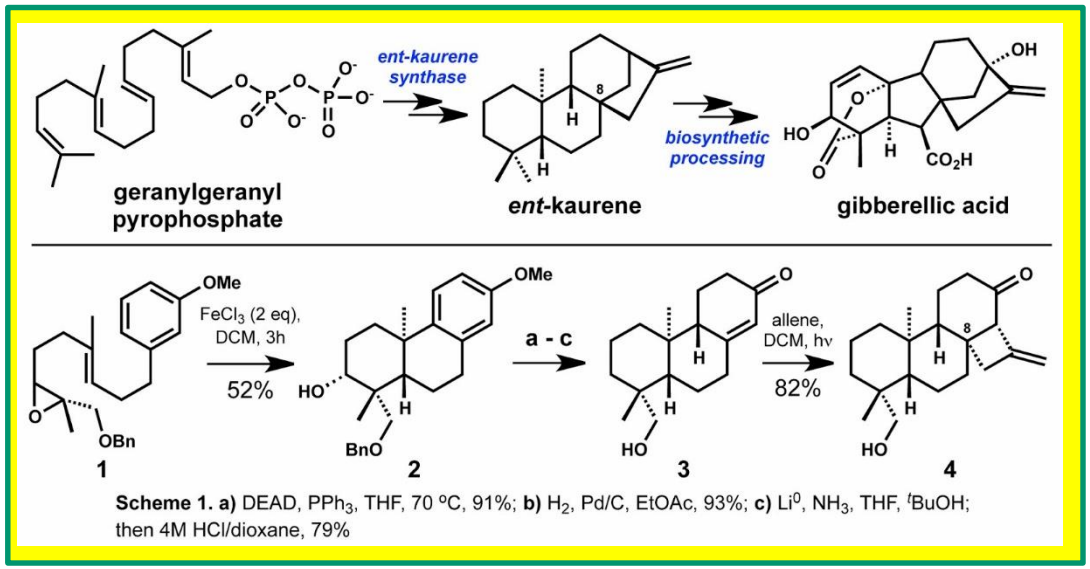


Steviol and the metabolic grid of glucosylation reactions resulting in formation of Reb D and Reb M. Top left the structure of steviol with emphasis on its functional groups. Reb D and Reb M are the two desired sweeteners (shown on green background). UGT91D2 has not been observed to glucosylate glucoside structures that harbor a glucose residue bound in a 1,3-glucosidic linkage. Formation of the 1,3-bond prior to formation of the 1,2-bond results in production of undesired side-products (shown on red background) [13, 15, 16]. UGT76G1 is known to glucosylate Steviol-13-O-monoglucoside (13-SMG), rubusoside, 1,2-stevioside and Reb D. In this study, 1,2-bioside, Reb G, Reb A and Reb E were identified as additional UGT76G1 substrates. UGT76G1 catalyzed glucosylation of Reb G and Reb A lead to the formation and structural elucidation of two new steviol glucosides Reb Q and Reb I

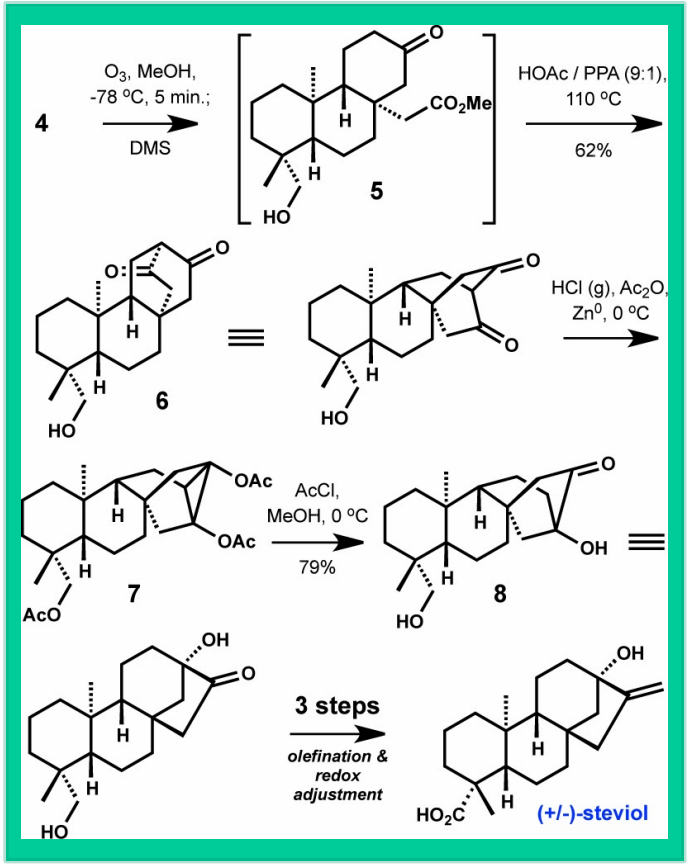
Microbial Cell Factories volume 15, Article number: 207 (2016)

Development of a Practical Total Synthesis of (+/-)-Steviol

Baran laboratory



Scheme 1. a) DEAD, PPh_3, THF, 70 °C, 91%; **b)** H_2, Pd/C, EtOAc, 93%; **c)** Li^0, NH_3, THF, ^tBuOH; then 4M HCl/dioxane, 79%



Enzymatic conversion of geranylgeranyl pyrophosphate (GGDP) affords ent-kaurene. The enone **3** was then obtained from **2** by a three-step sequence involving elimination of a secondary alcohol, hydrogenolysis and Birch reduction/isomerization. In the subsequent operation, a critical allene [2 + 2] photocycloaddition installed the hindered C8 quaternary center of the advanced cyclobutane intermediate **4**.

Ozonolysis of 4, when conducted in methanol, induced fragmentation of the strained cyclobutane framework to generate the intermediary methyl ester 5. Next, the [2.2.2]bicyclic system of 6 was fashioned by exposure of 5 to forcing acidic conditions and subsequent reductive cyclopropanation in the presence of acetic anhydride led to the advanced diacetate 7. Finally, controlled fragmentation of 7 with methanolic hydrochloric acid, followed by an expedient methylenation/oxidation endgame sequence produced fully synthetic steviol in only 17 total steps starting from geranyl acetate.