Drug Development
A Multidisciplinary Process

Ulf Preuschoff/Siegfried Schäfer

Solvay Pharmaceuticals

Hannover

Solvay Pharmaceuticals R&D Sites

Brussels, Belgium

Hannover, Germany

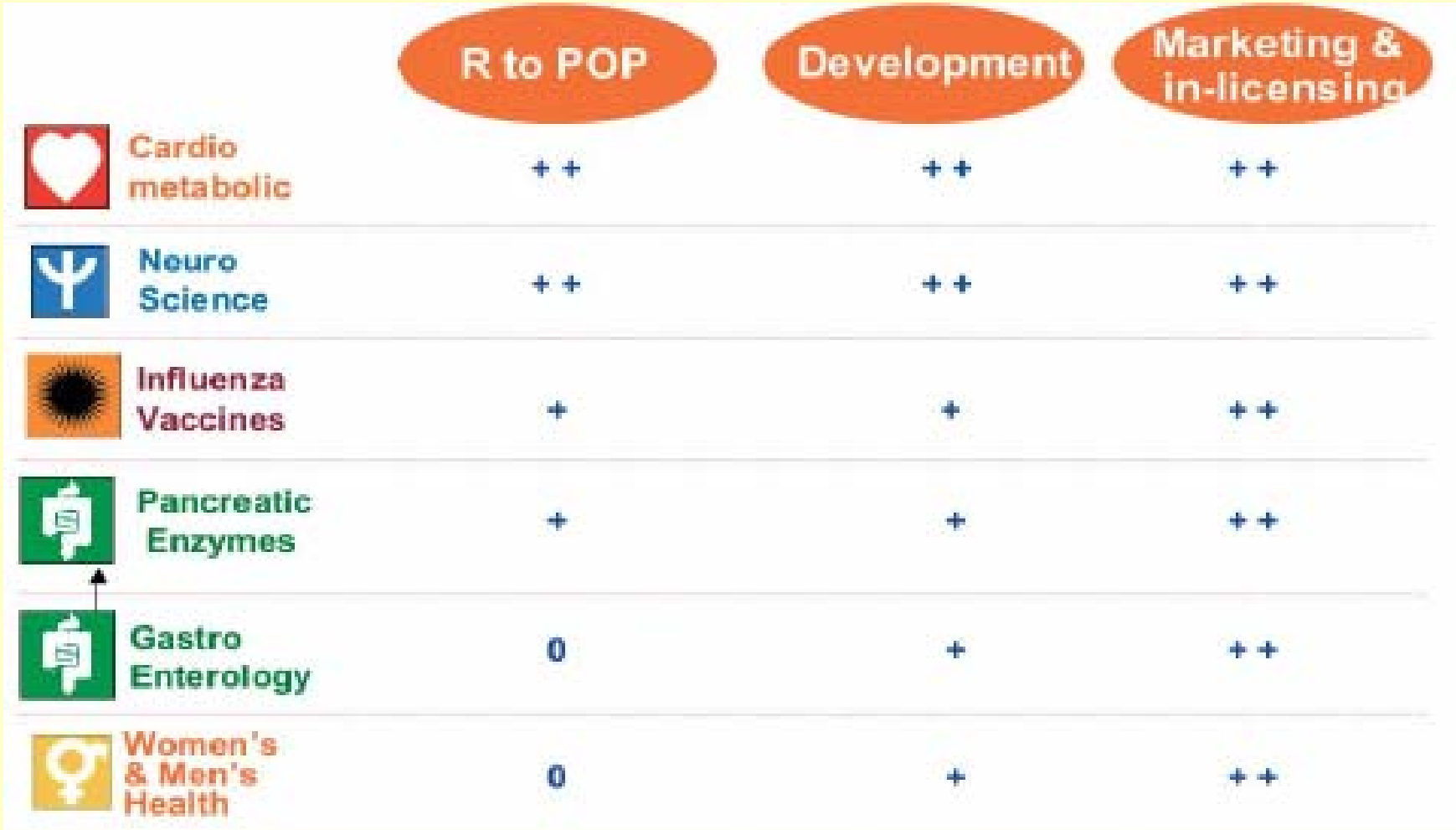
Fournier, France

Tokyo, Japan

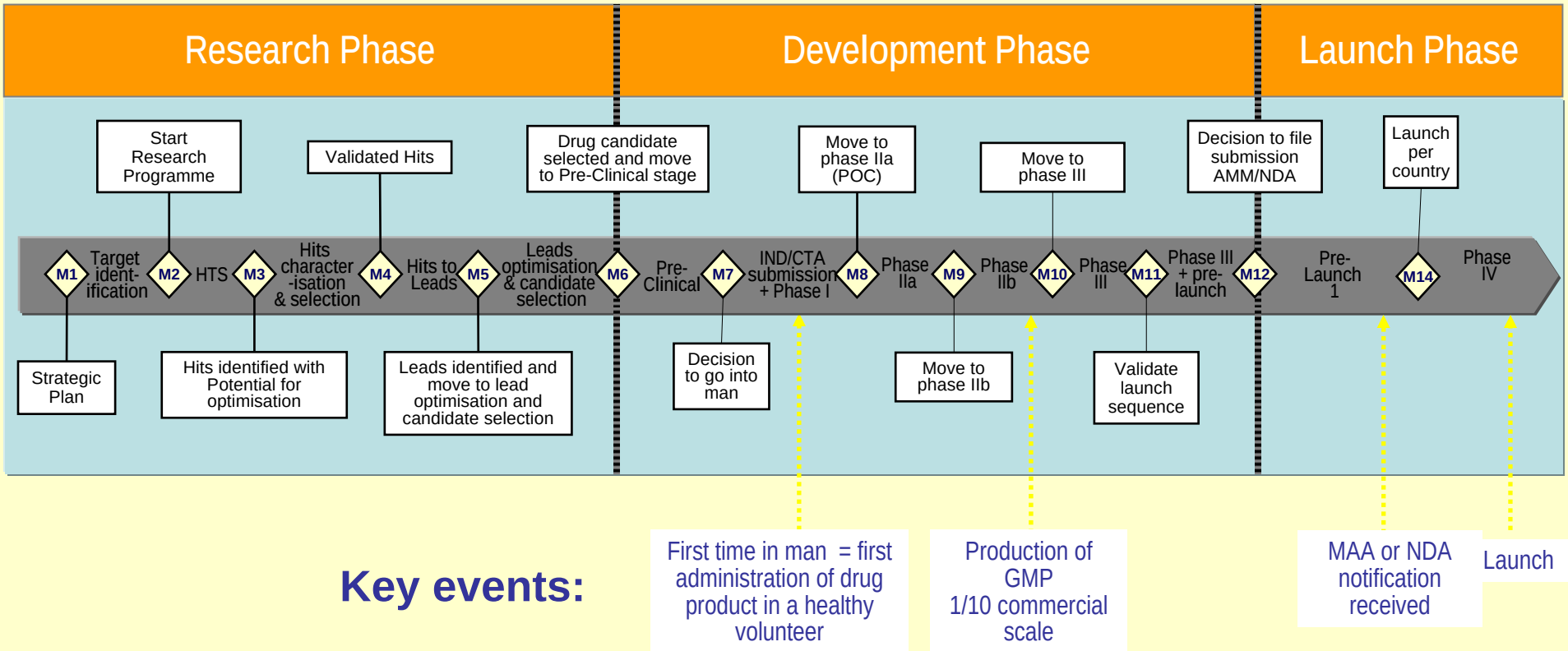
Marietta, USA

Weesp, The Netherlands

Solvay Pharmaceuticals Therapeutic Areas



Drug Development Scheme Management Decision Points

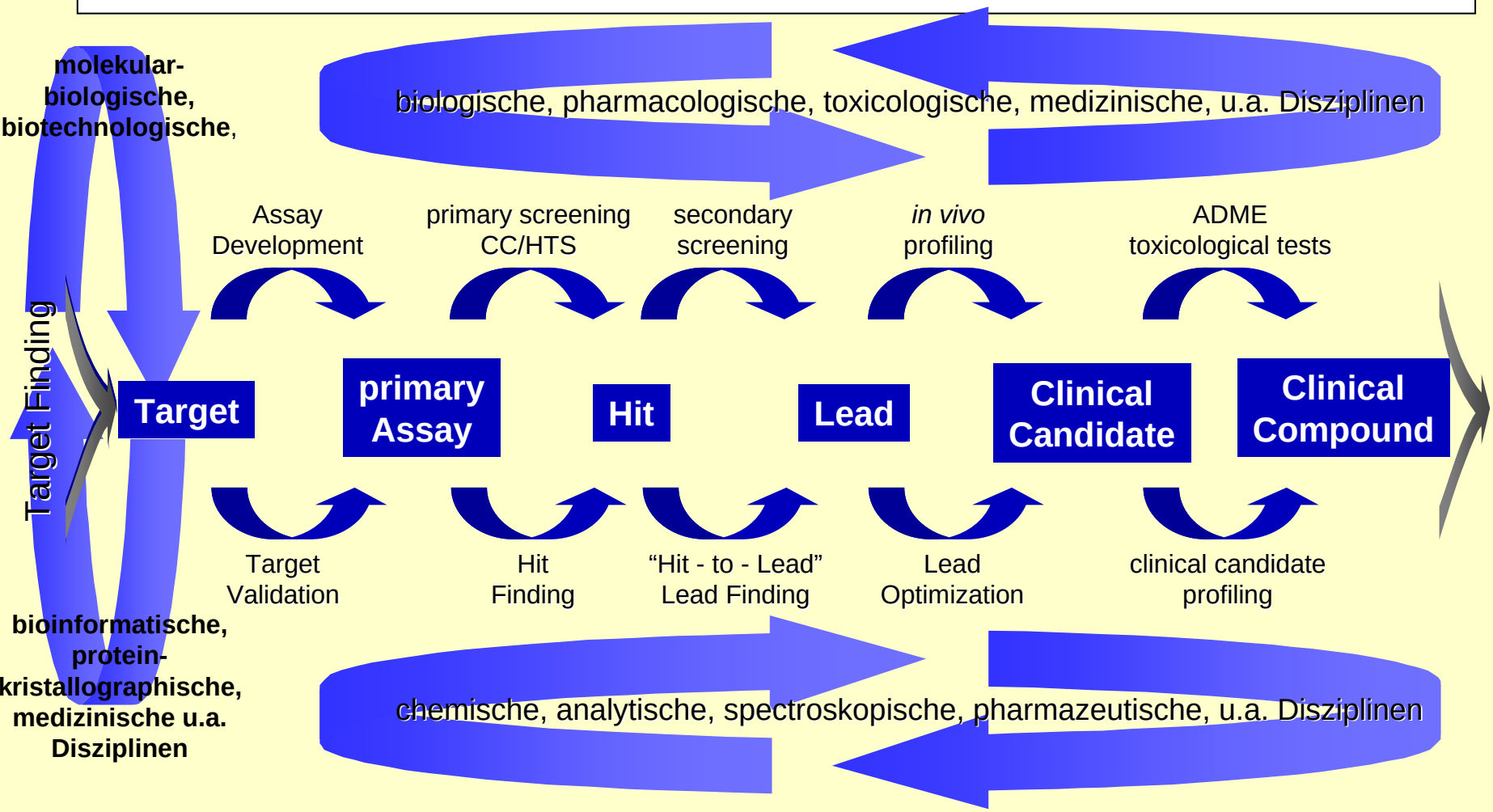


Key events:

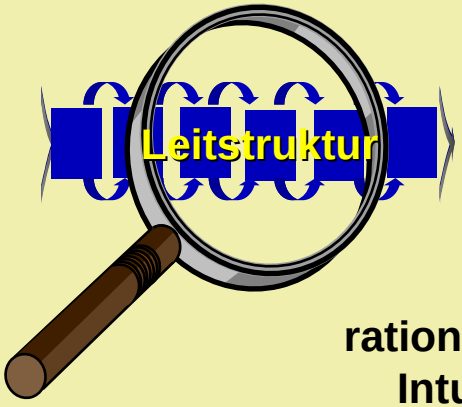
Research and Development

Drug Discovery Orchestra

Präklinische Phasen, Prozesse und beteiligte Disziplinen



Screening



rationale Idee
Intuition
Auswahl

Synthese
"Bibliotheken"

Synthese
"Substanzen"

Substanzanbieter
Naturstoffbanken

CADD

Spektroskopie
Analyti

HTS
Primär-
screening

Assay

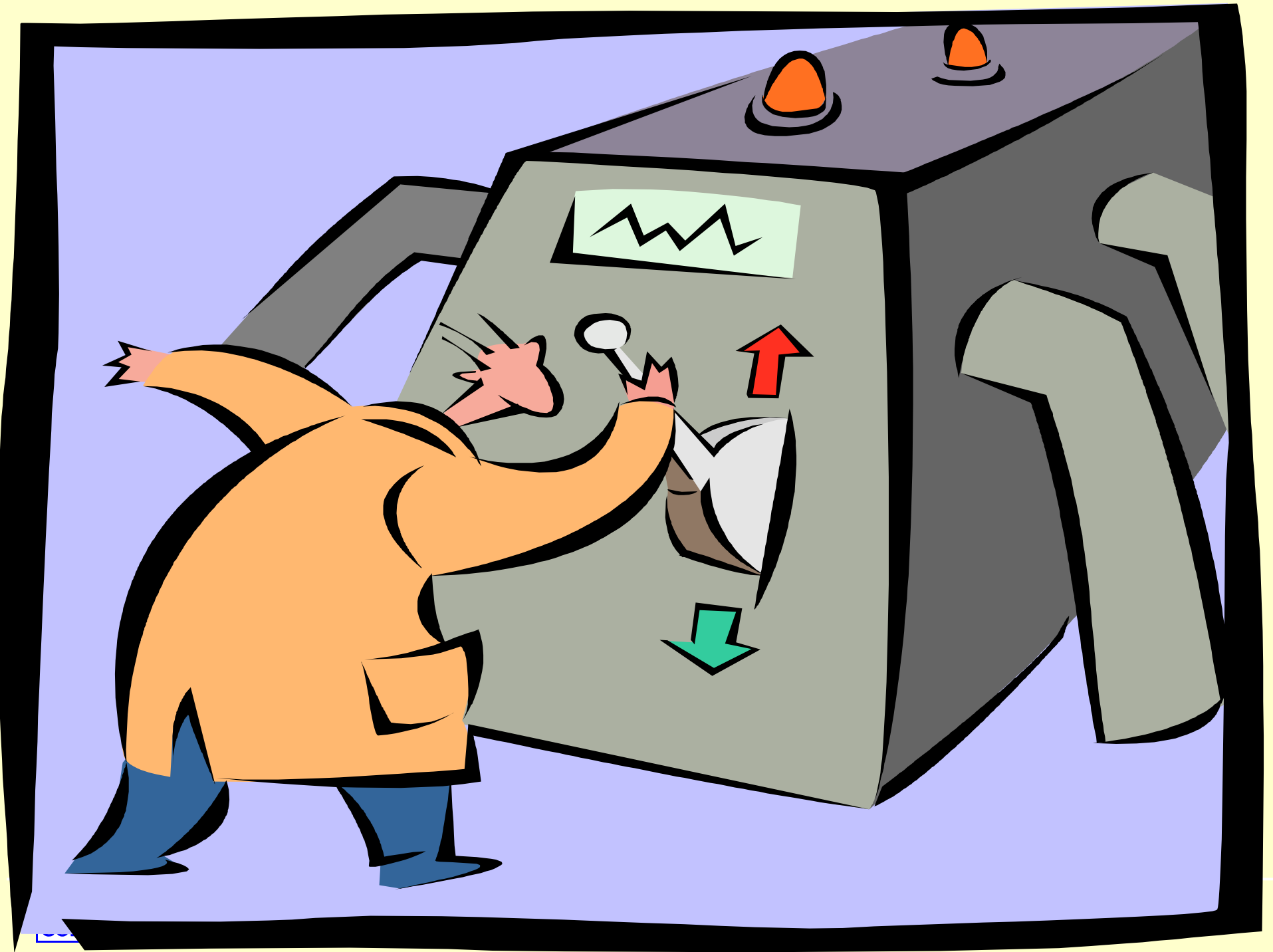
CADD

Sekundär-
screening

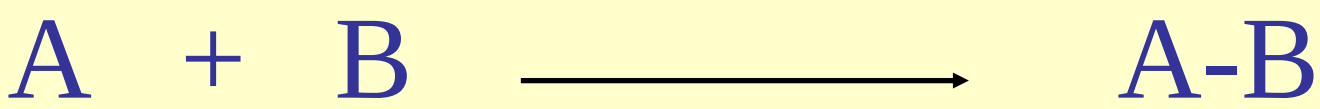
Chemische und
pharmazeutische
Entwicklung

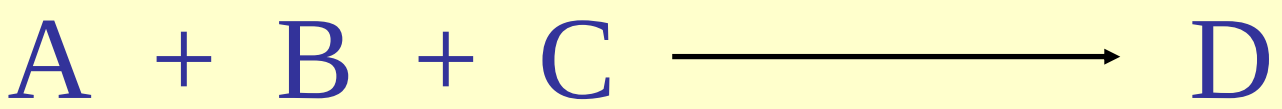
Drug Development: A Multidisciplinary Process

1. Target selection
2. Assay development and validation
3. In silico chemistry, properties (ROF etc), in silico ADME, structure based design
4. Combinatorial Chemistry, compound selection from available stock
5. Medicinal Chemistry
6. HTS, MTS
7. In-vitro Pharmacology: Receptor binding, functional tests, isolated organs, &c &c
8. In-vitro ADME: Solubility, Membrane passage, Cytochromes, Metabolic Stability

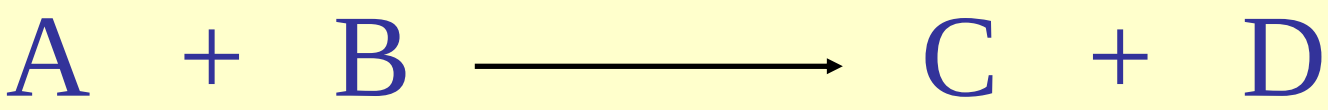


Combinatorial Chemistry

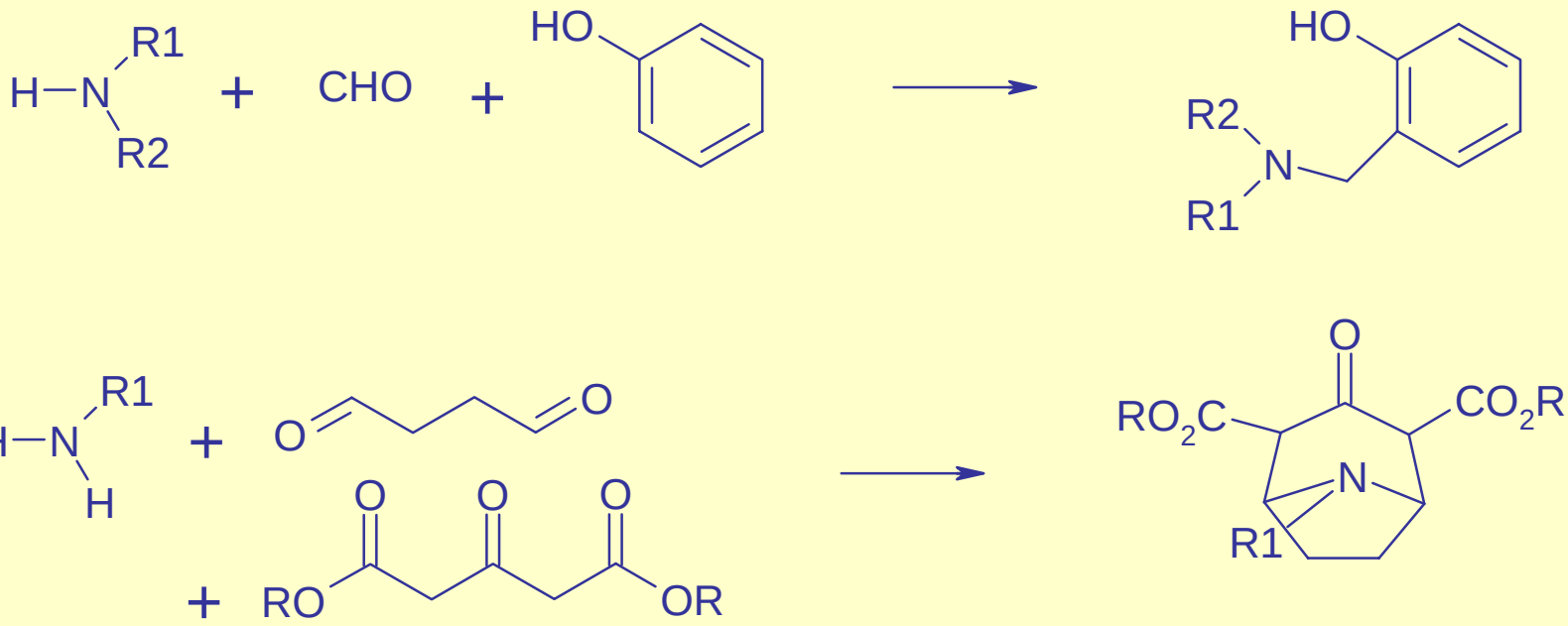




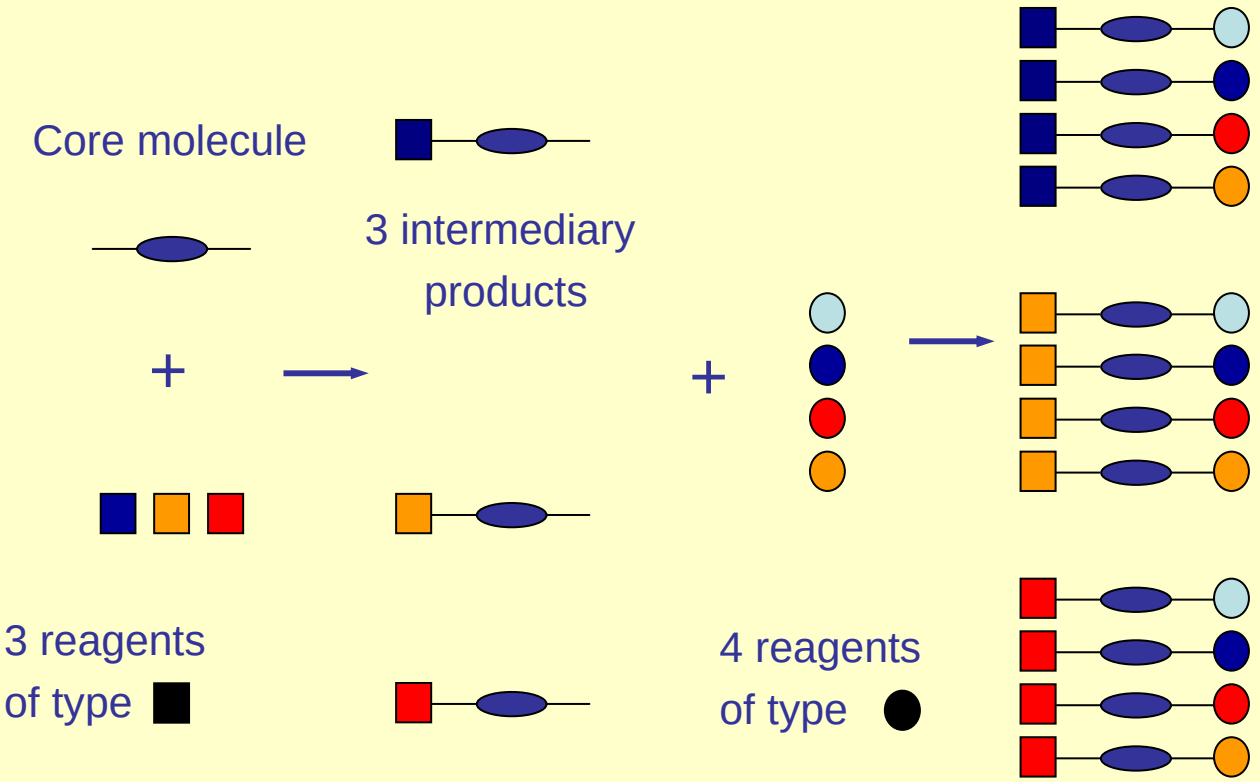
NOT



Mannich Chemistry:



Combinatorial Chemistry



Result: library with 3 x 4 = 12 substitute core products

Solvay Arqule Alliance

RESULTS

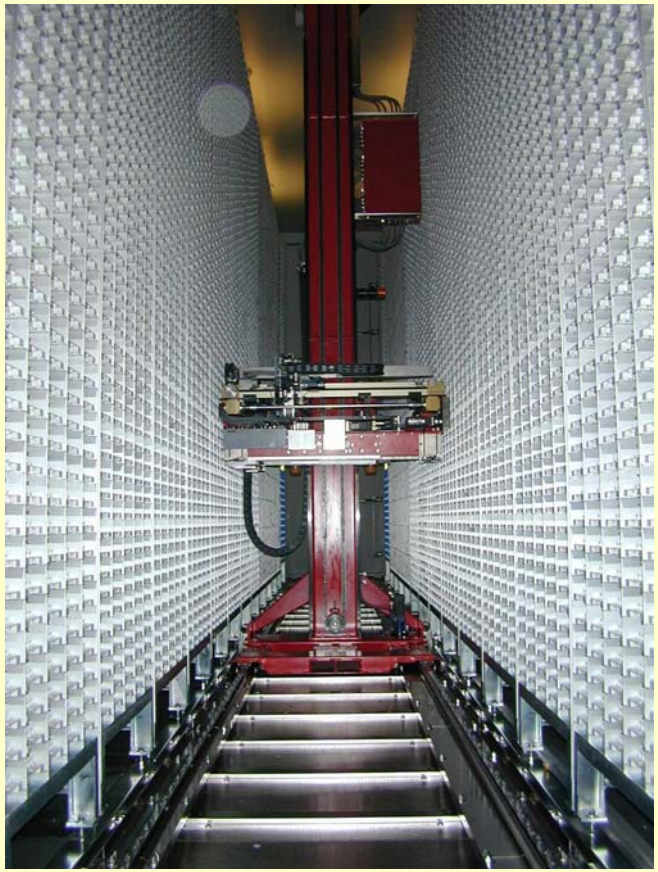
- **Arqule**
  - **Delivered 125,000 exclusive compounds**
  - **20,000 exclusive compounds/year**
  - **200,000 screening compounds/year**
    - **TOTAL >1,000,000 COMPOUNDS**
  - **Diversified chemical input**

Drug Development: A Multidisciplinary Process

- REMP Storage System

Type: “Mixed Warehouse”

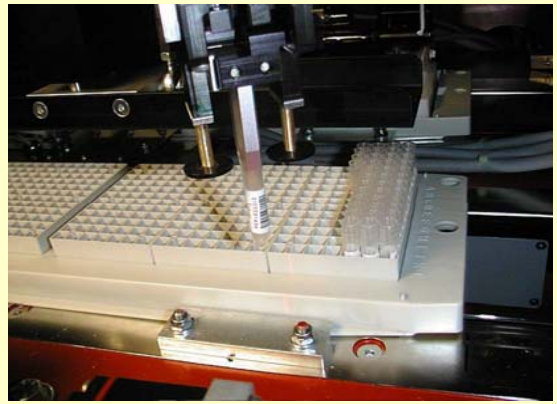
- Size: length 17m; width: 3.8m; height: 5.5m
- Storage temperature: +4°C
- humidity: < 20%
- Stores standard deepwell plates, microtiter plates, flasks and vials
- Capacity: 5 million compounds in 96 well format.



Drug Development: A Multidisciplinary Process

Storage devices and Handling

Plates	Flasks	Tubes
65 P/h	130 F/h	160 T/h



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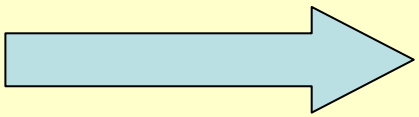
Drug Development: A Multidisciplinary Process

9. Early formulation work
10. In-vivo Pharmacology
    - Mechanistic model
    - Disease oriented model
11. In vivo ADME: PK/PD, Culex
12. Orientating toxicology/safety,
13. Toxicogenomics/pharmacogenomics
14. Pharmaceutical Characterization
    - Classic adjuvants
    - Nanosizing, Cyclodextrins, PEG, Liposomes
15. GLP Toxicology and GLP ADME
16. Chemical and pharmaceutical development
17. Clinical Phases 1 and 2
18. Full Development

Drug Discovery Paradigms in Pharmaceutical Industry

- **Small Molecules with high oral bioavailability**
- **Advantageous ADME profile, ROF compliance, membrane passage**
- **Good chemical and biological stability**
- **Short and cheap synthesis, easy upscaling**
- **No toxic or allergic reactions**
- **Blockbuster potential**



No Biopharmaceuticals !

What is a Biopharmaceutical?

Biopharmaceuticals

Defined by Production:

- Extraction from biological matrix, e.g. growth hormone from human bodies
- Proteins by chemical synthesis: Only for small proteins
- Fermentation: Most important
  - ✓ E.coli
  - ✓ Mammalian cells, CHO or BHK cells
  - ✓ Insect cells
  - ✓ Yeast and fungi

Biopharmaceuticals or Bioproducts

- Natural products, extracts: Baldrian?
- Pancreatic enzymes as Creon, Pancreatin?
- Recombinant Lipase, Amylase, Proteases
- Penicillins?
- Erythromycin A and other macrolides?
- Motilides, semisynthetic macrolides with 14 membered ring structure and 17 stereocenters from EA?
- Monoclonal antibodies
- EPO
- Vaccines

Biopharmaceuticals or Bioproducts

⇒ Bioproducts are derived from fermentation

Contracting of special problems for development:

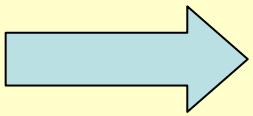
- **Fragments originating from producing microorganisms as potential impurities**
  - **Cell material as membrane proteins, sugars &c&c**
  - **DNA fragments (picomolar!)**
  - **Often mixtures: glycosylation structure, heterogeneity N-terminus**
- **Specific patent issues: Bioproduct has been invented already by nature, protection only for newly identified product with provided production (isolation) process**
- **Upscaling often cumbersome, high COG**

Biopharmaceuticals: Example Infliximab

- In 1994 Centocor offered Infliximab for licensing
- Impressive efficacy against TNF-a and in arthritis pharmacology models
- Safety: 30mg/kg single dose infusion and 90mg/kg multi dose infusions to chimpanzees are „safe“
- Worst case patient selection, 10mg/kg as single dose
- Dose scheme (twice weekly) decided upon based on plasma levels in humans
- 100% responders
- Side effects: Urinary tract infections, bronchitis, pharyngitis, urticaria, eczema, pruritis

Biopharmaceuticals: Infliximab

Would you buy it?

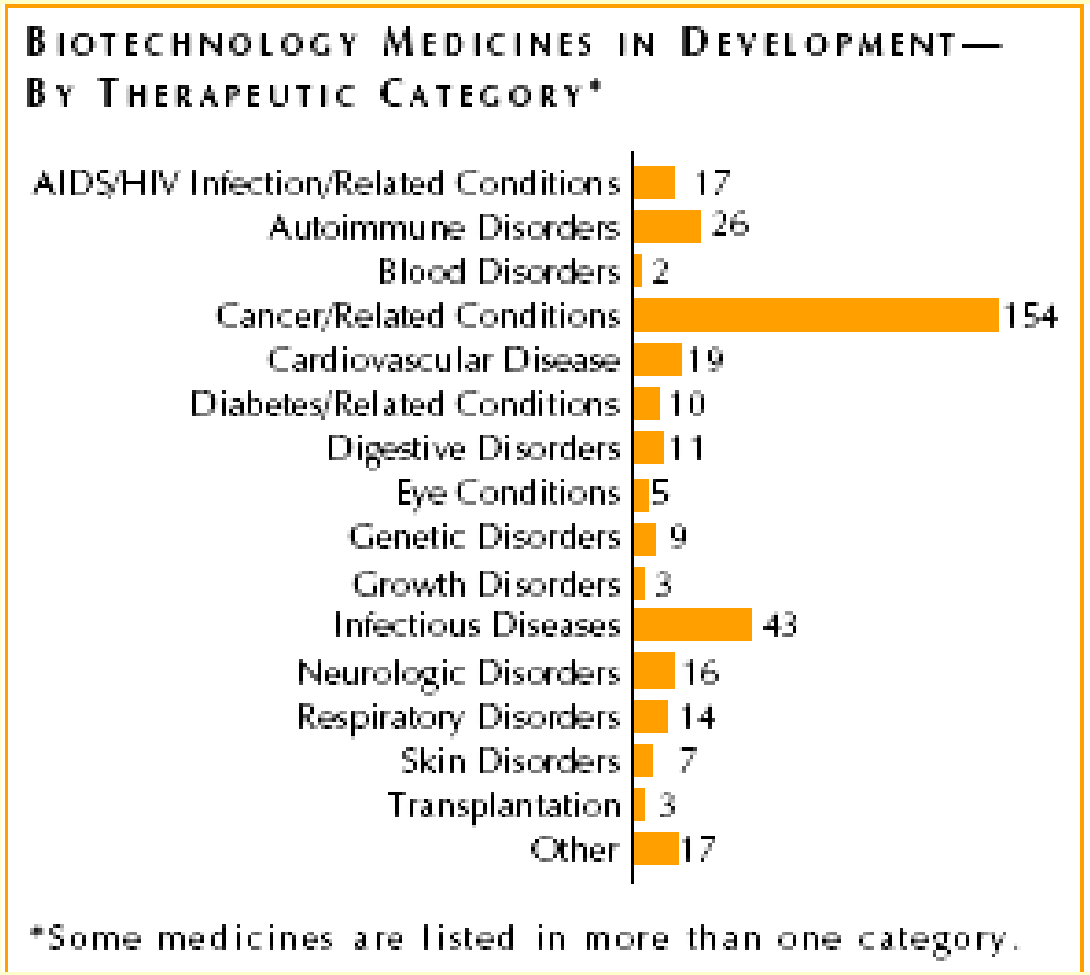


Today Blockbuster Drug
More than 1 Billion USD sales
Recently FDA approval for maintenance in UC

Biopharmaceuticals

- There is no investment in pharmaceuticals just from altruistic motives
- Without economic success there will be no sustainable advantage for the patient
- Biopharmaceuticals must offer high value for the patients
  - Often life prolongation
  - Generally used in „hard“ indications
  - Cancer, MS, Rheumathoid Arthritis, Infection
  - Vaccines: Flu pandemia expected!

Therapeutic Indications for Biopharmaceuticals



Biopharmaceuticals: Market potential

- 50 BUSD sales worldwide
- 80 NBE‘s approved
- EPO with 9 BUSD sales blockbuster drug
- Monoclonal AB‘s 5 BUSD
- Interferon ß 3 BUSD
- Ca 300 NBE‘s in clinical development
- Ca 350 NBE‘s in preclinical development
- Double digit growth rates

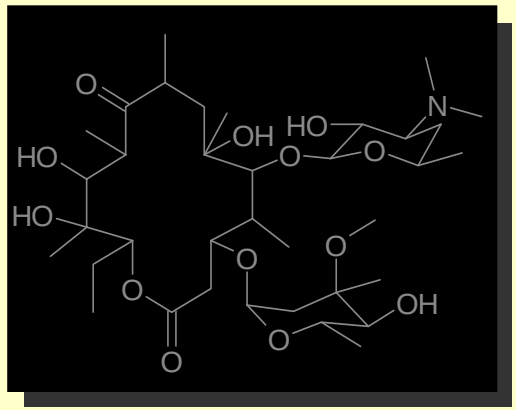
Biopharmaceuticals: Market potential

Year	2000	2001	2002	2003	2004
Biopharmaceutical sales	23	27	33	40	48
Growth (%)	16	19	23	21	20

Example: Erythromycin A

Erythromycin A

- antibiotic compound
- stimulates upper GI-motility and phase III activity (Itoh et al. 1984)
- erythromycin acts as a motilin agonist (Peeters et al. 1989)



Motilin

- 22 amino acid peptide
- gut hormone involved in stimulation of upper GI-motility Phase III of Migrating Motor Complex (Brown et al. 1966, 1972)

Erythromycin A

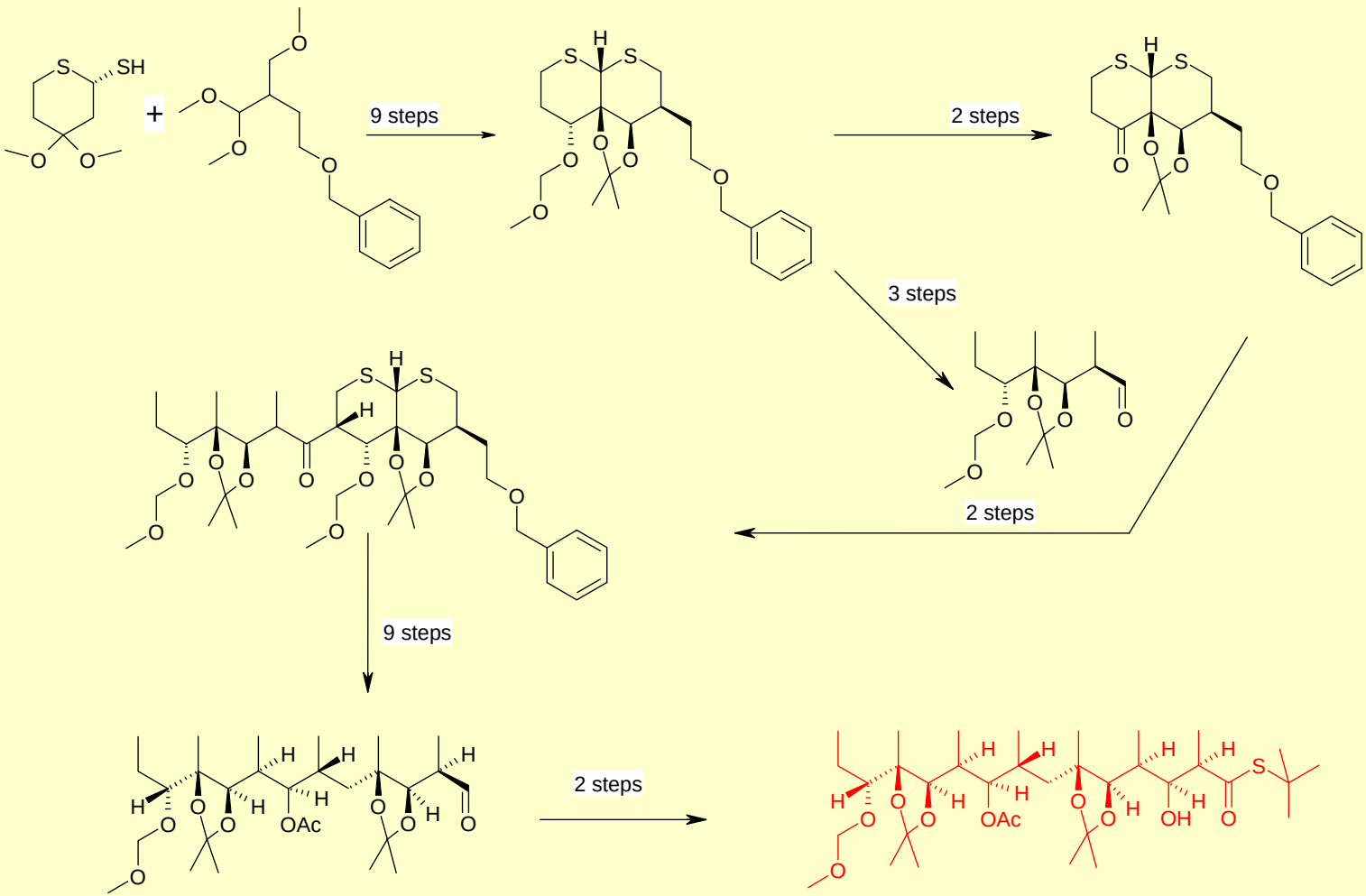
- **Macrolide antibiotic produced by certain strains of streptomyces erythreus as defense weapon against bacterial infections**
- **Long time medical use, safe compound**
- **Well known GI side effects caused by motilin agonistic effects**
- **Natural compound with 17 stereocenters, 2 glycosidic linkages and 5 hydroxy functions**
- **(3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-((2,6-Dideoxy-3-C-methyl-3-O-methyl-a-L- ribo- hexopyranosyl) -oxy) -14- ethyl-7,12,13-trihydroxy - 3,5,7,9,11,13-hexa methyl-6- ((3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo- hexopyran osyl)oxy)oxacyclotetradecane-2,10-dione.**

Erythromycin A

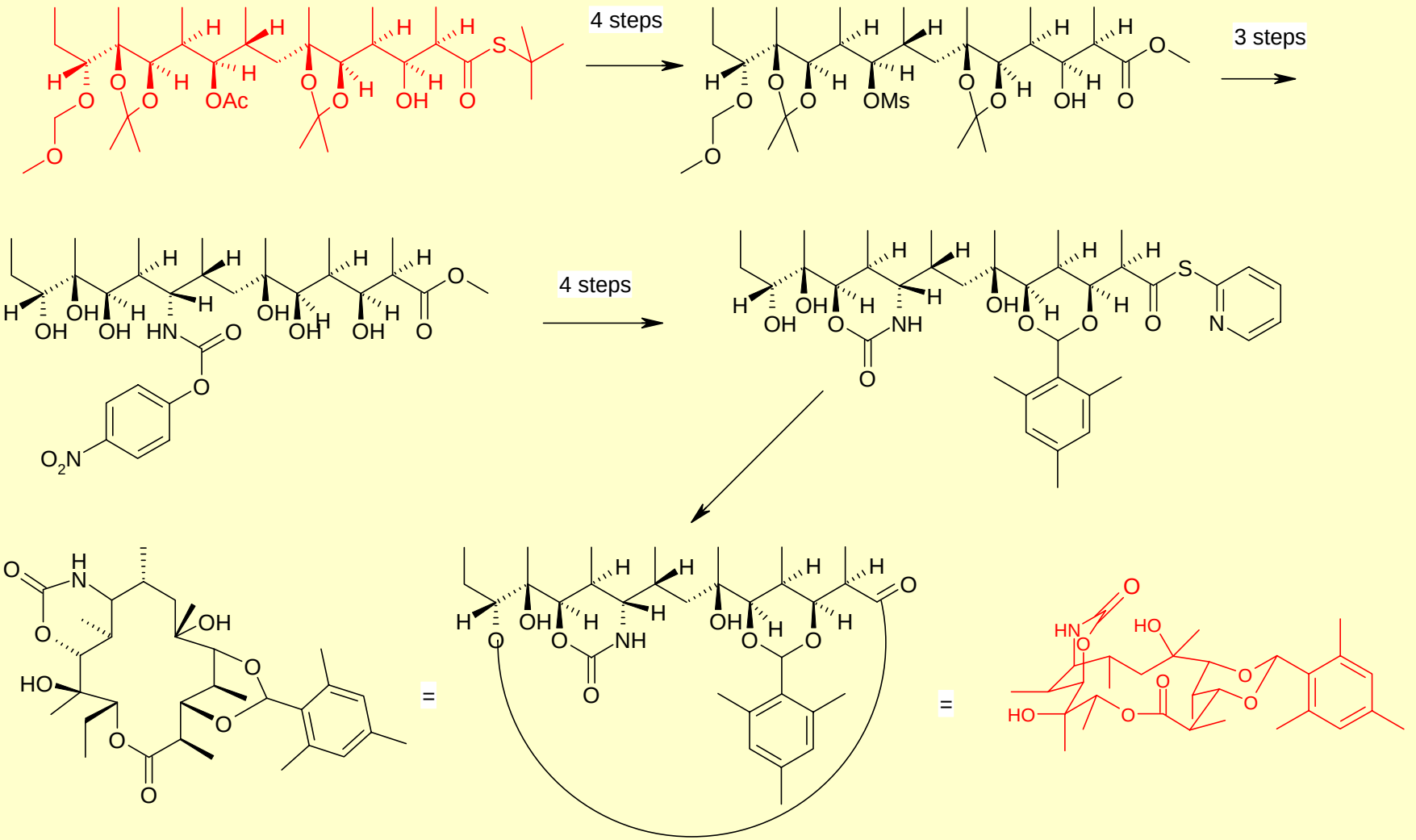
- Not „drug-like“, natural product
- Not compliant with Lipinsky‘s „Rule of five“
- Not stable in acid, poorly bioavailable in rats
- Complicated molecule, very complicated synthesis
- Active transport, orally bioavailable

Total Synthesis of Erytromycin A

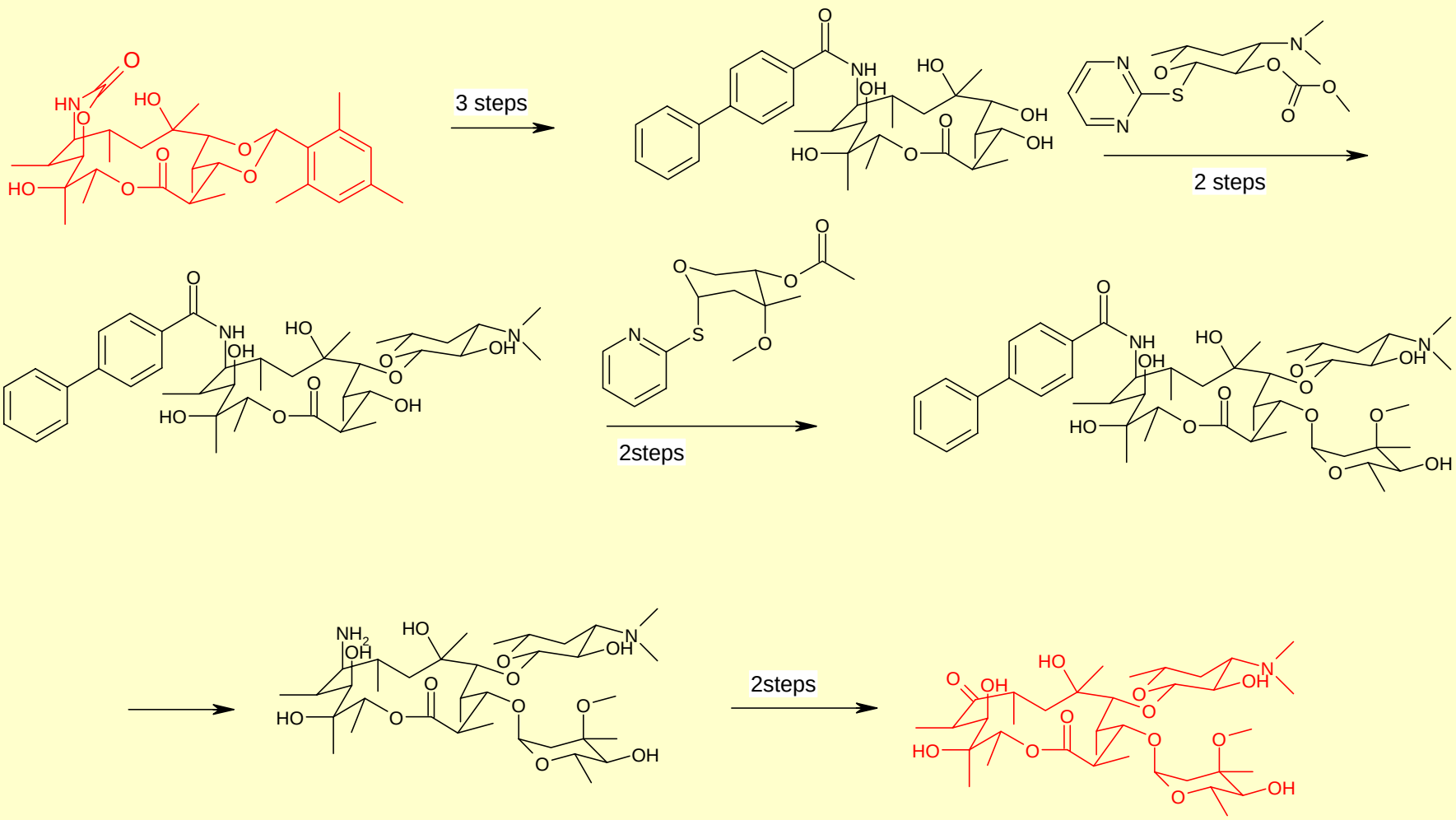
Woodward et al, JACS 1981



Total Synthesis of Erythronolide A



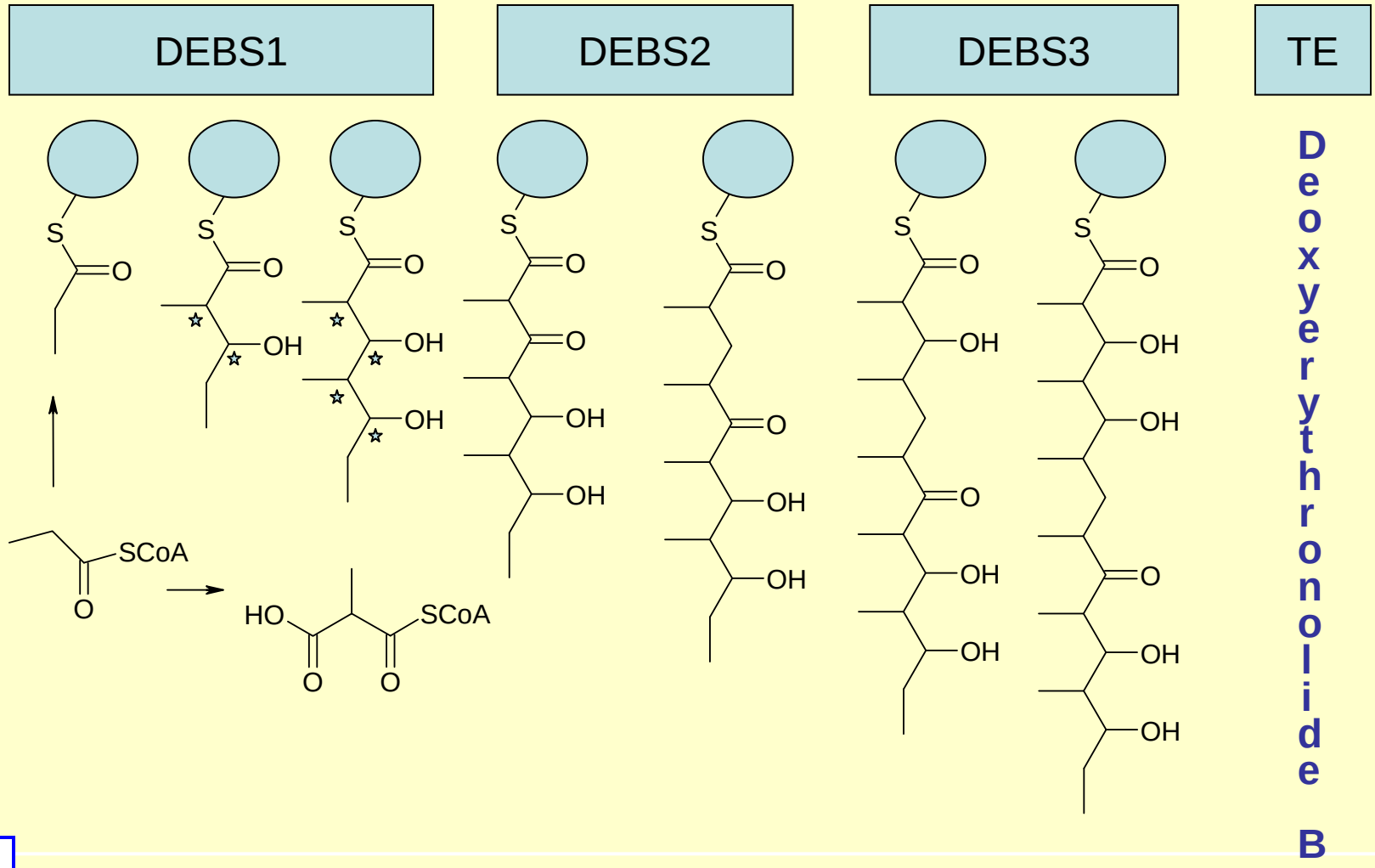
Total Synthesis of Erythromycin A



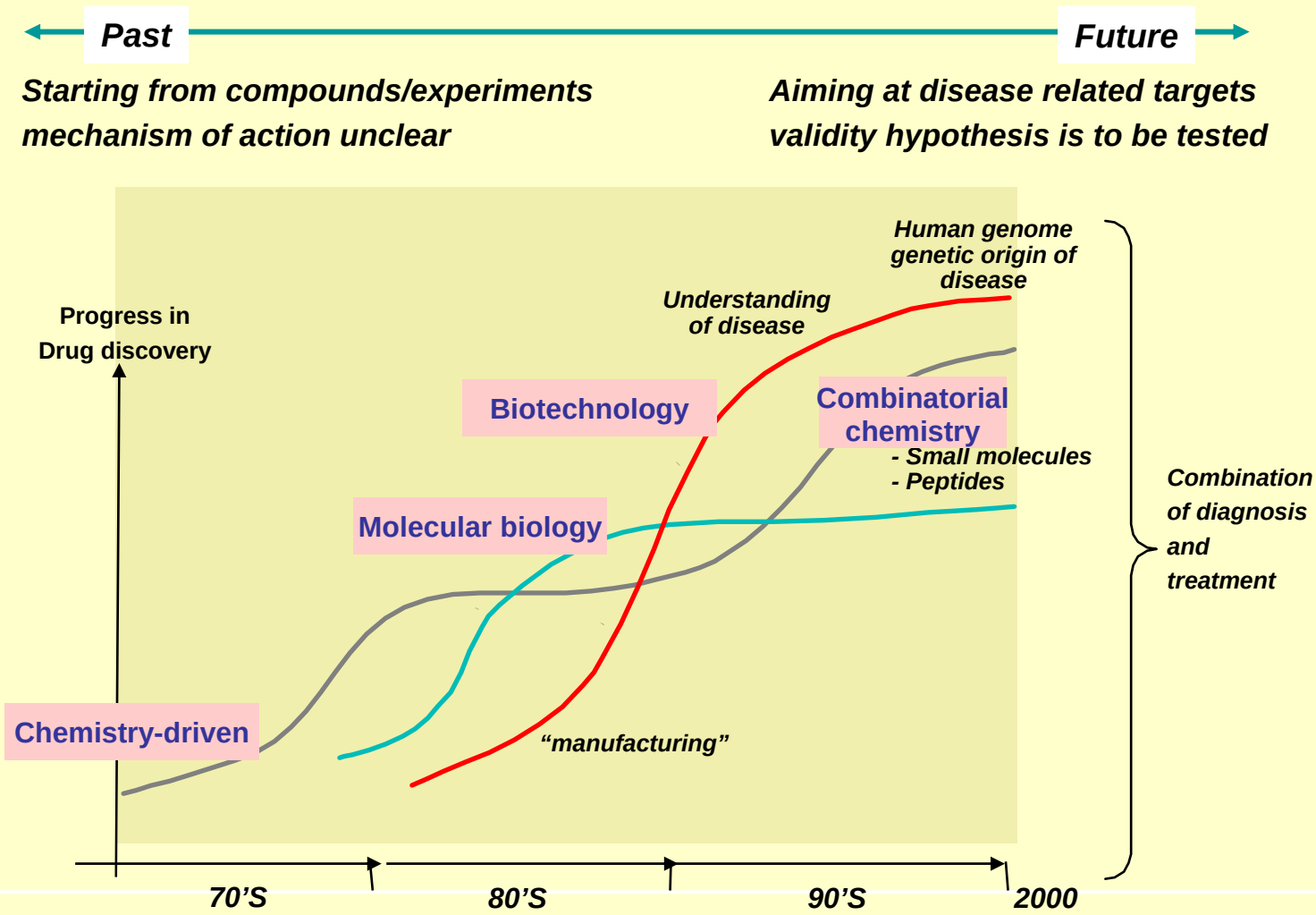
Erythromycin A

Erythromycin A is available in 25kg packs, 67USD/kg bulk

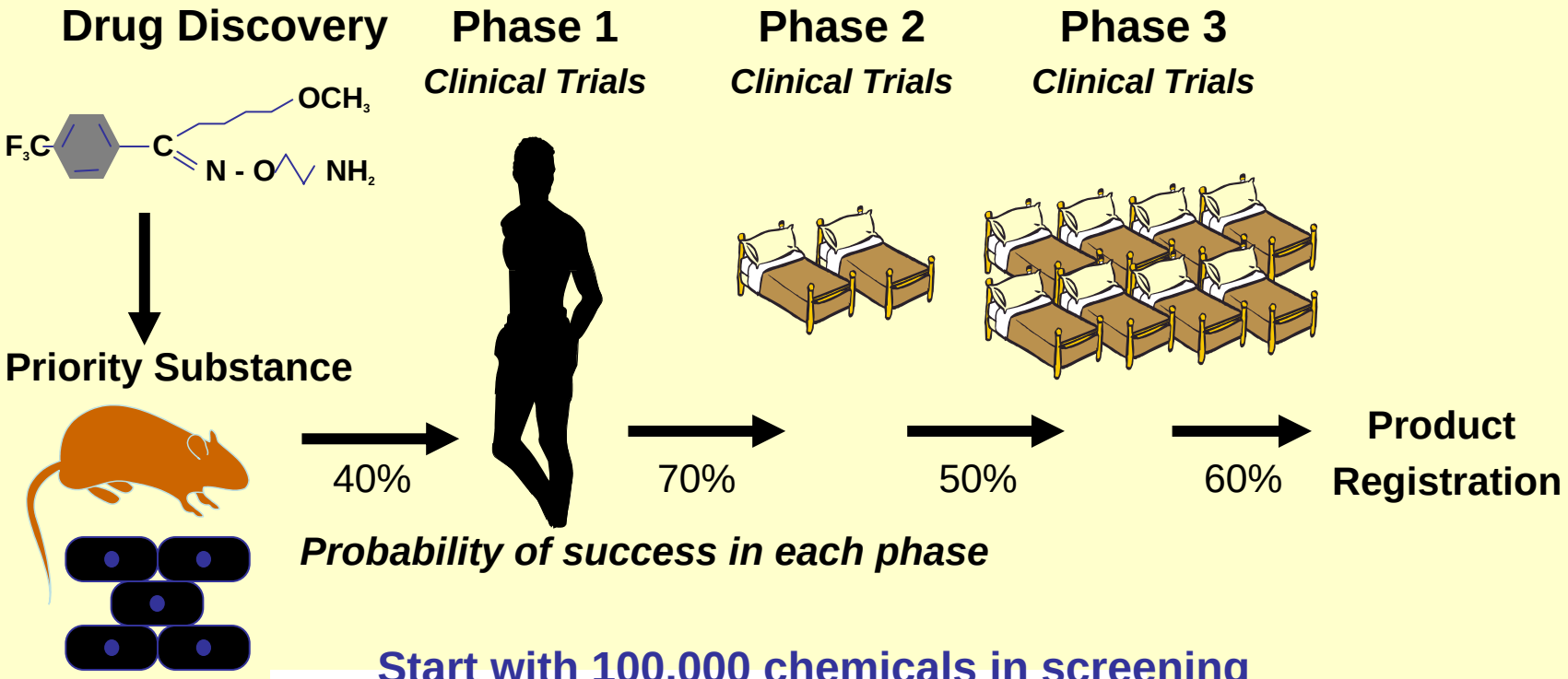
Biosynthesis of Erythronolide B



Solvay Pharmaceuticals: Research



Clinical Candidate Survival Rates



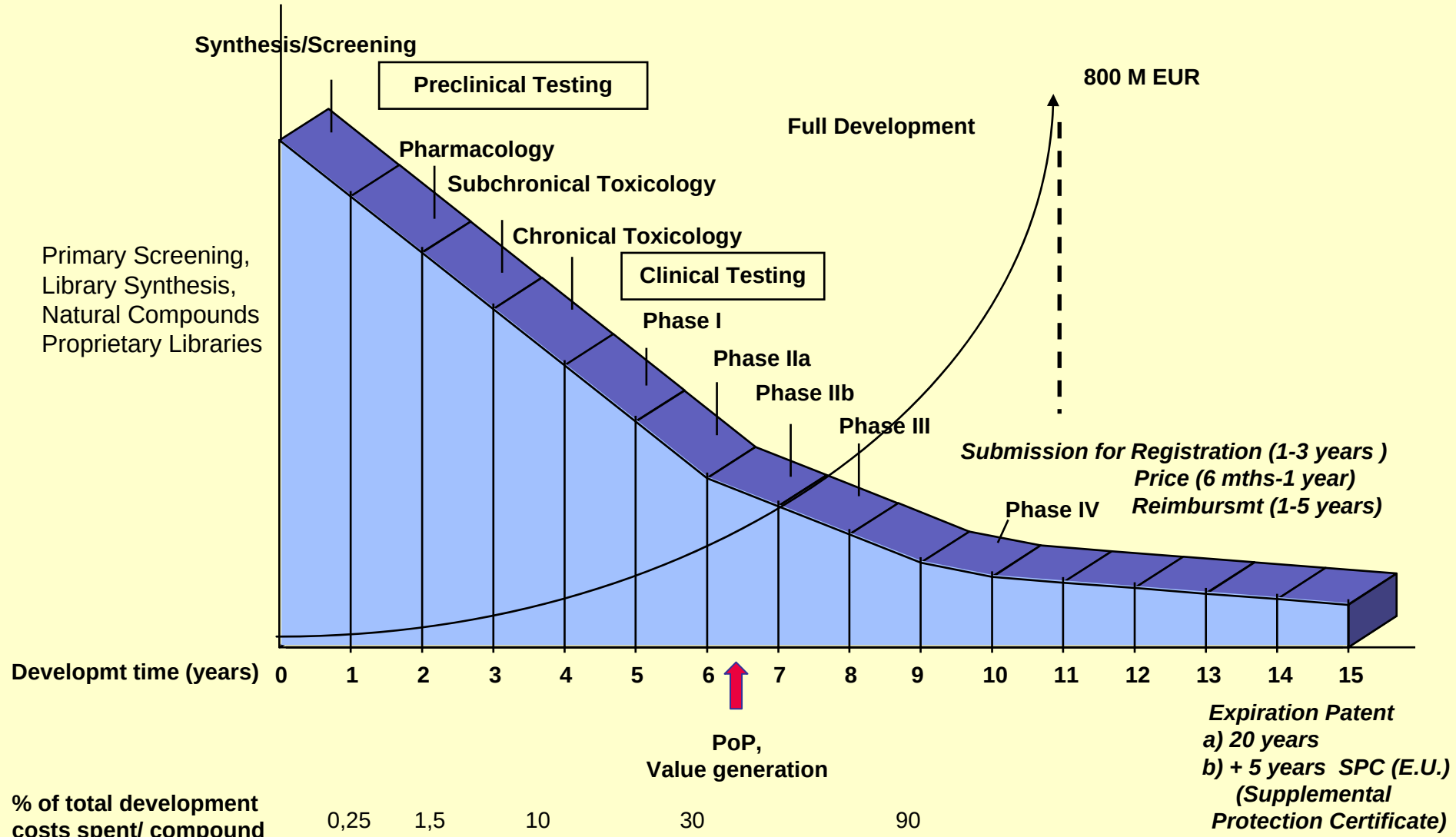
Start with 100,000 chemicals in screening
Only 8% survive after PS stage
Total R&D time 10 years or more
Cost per product $US 800M

Clinical development

	Phase I	Phase II	Phase III	Total
Mittlere Anzahl von eingereichten Studien	20	5	10	35
Mittlere Anzahl von Individuen	427	639	3348	4323

Aus: CMR Intern. 2000

The lenghthy process of drug development reduces the effective patent protection time



Thank you very much

For your attention!