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Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

RESOURCES NEEDED AND CHEMICAL METHODS USED IN CURRENT API SYNTHESIS

A medicinal chemist's perspective

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Drug Lifecycle Control in Subsaharan Africa
Workshop, 29 August - 3 September 2022
Arusha, Tanzania

Contents

- Basic requirements, financial considerations
- APIs
- Synthetic methods in API production
- Two examples
- Challenges and limits

Should sub-Saharan Africa make its own drugs? McKinsey report 2019

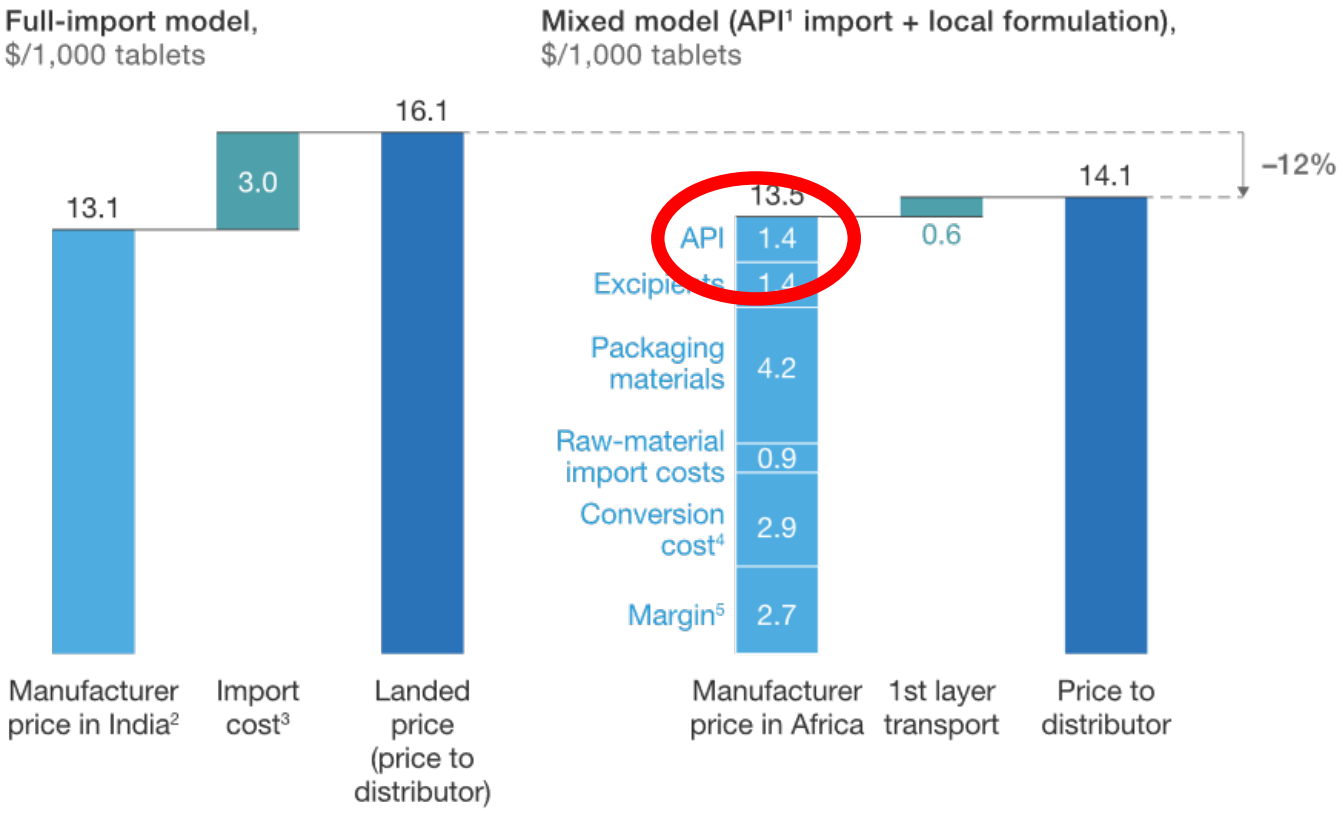
- Five lessons for creating a sustainable pharma sector in sub-Saharan Africa:
  - focus on quality
  - production capacity (or scale)
  - regional hubs
  - drug-product formulation
  - value-chain effects

- Cutoff for output to be cost competitive with India:
  - depends on product type
  - tablet-based product: approx. 500 million tablets

https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs

Should sub-Saharan Africa make its own drugs? McKinsey report 2019

- Model comparison: Indian imports vs production in Ethiopia for one OTC drug



https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs

Should sub-Saharan Africa make its own drugs? McKinsey report 2019

- Current API production: very scale sensitive; hard; requisite chemicals sector not in place
  - → 10-15% costlier than imports from India
  - → drug-product formulation is better bet
- Modern API production: improved process chemistry (costs reduction 5-35%), continuous manufacturing (cost reduction 10-25%), modular plant design (faster construction of the plants)
  - → adopt cutting-edge technologies without having to replace existing technologies and protocols

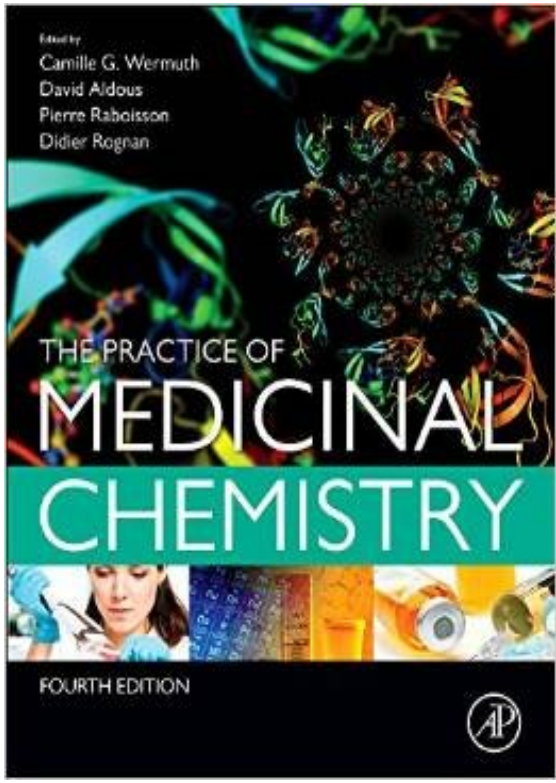
https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs

Active Pharmaceutical Ingredients (APIs)

Characteristics of an ideal API

- new chemical entity for patentability and registration
- new mechanism of action to prevent categorisation with old drugs
- max. four-step synthesis with, e.g., no heavy metal catalysts and no environmentally problematic waste
- no chromatographic purification steps; purity > 99%
- stable up to 70 °C even in humid air and towards light
- solid-state properties (crystalline, not polymorphous, not hygroscopic) that make it a perfect partner for (tablet) compaction

see:
C. G. Wermuth (Hg.)



Characteristics of an ideal API

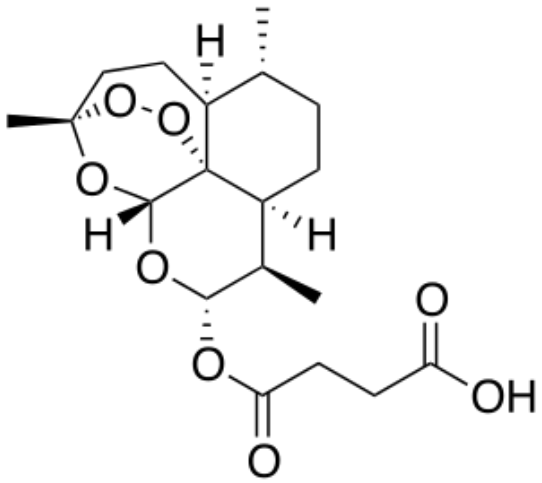
- solubility in water > 0.01 mg/mL; sufficient for the production of stable blood-isotonic solutions
- oral bioavailability > 90% with no interindividual variation
- very high activity (IC50 < 1 nmol/L, MIC < 1 mg/mL) and pharmacokinetic profile enable once-a-day-dosage at 5-10 mg

- Bioavailability and metabolism rather predictable because of low variety of absorptive and metabolic processes
- Toxicity and effects hardly predictable because of large variety of effects and potential targets

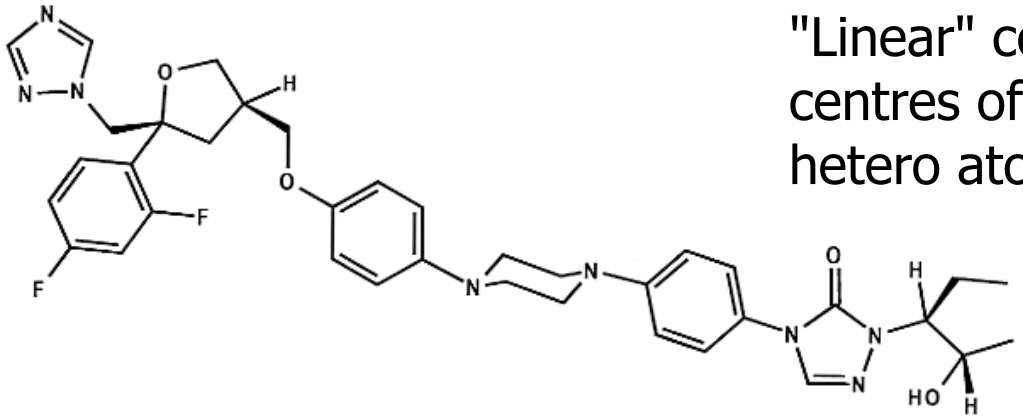
The chemical "toolbox" for API synthesis

- Typical build of modern APIs
- Reactions used most frequently

Natural or synthetic?

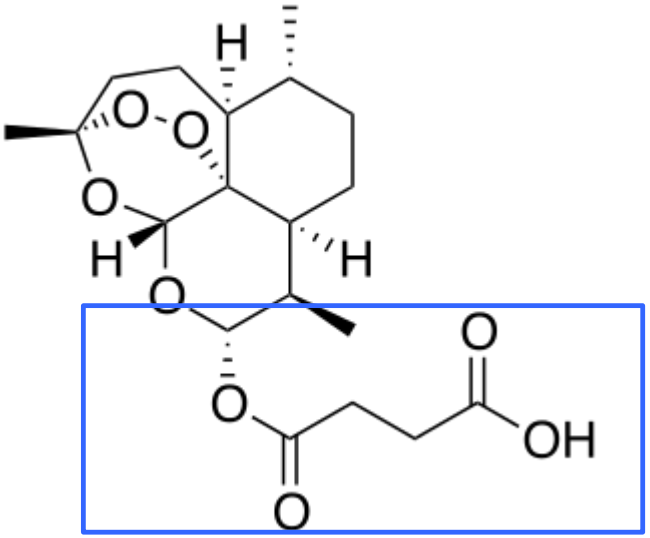


Artesunate. Natural compound. Anulated rings, many centres of asymmetry, most frequent hetero atom: oxygen.

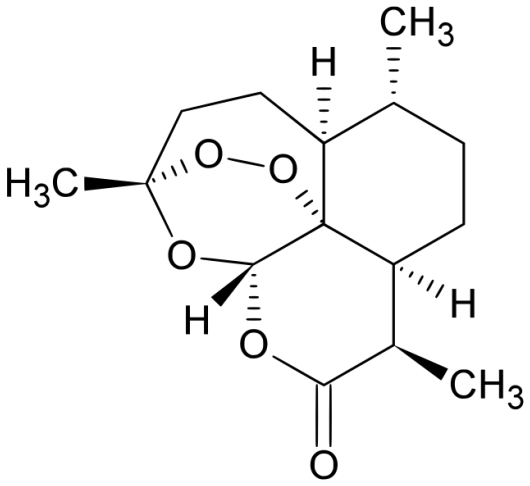


Posaconazol. Synthetic. "Linear" connection of rings, few centres of asymmetry, most frequent hetero atom: nitrogen.

Natural or synthetic?



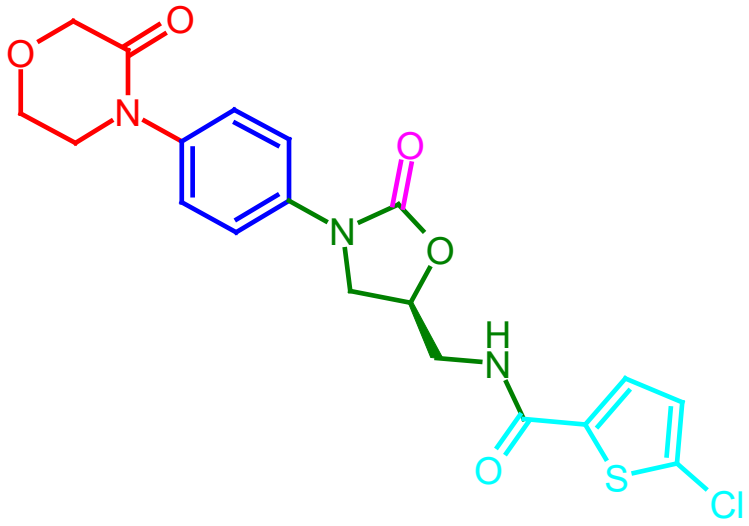
Artesunate.
Derivative of natural compound.



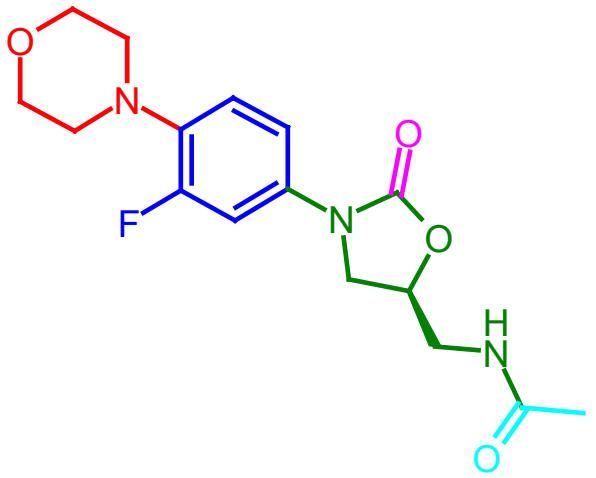
Artemisinin. Natural compound.
Not stable enough.

Properties of a typical med chem compound and synthesis

- physicochemical properties:
  - Mr 350-550
  - 4-6 HBAs, 1-2 HBDs
  - 6-8 NRot
  - clogP 3.5-5.5.
  - TPSA 60-90 Å2
  - 1-2 asymmetric centres
  - 30-50% of C atoms sp3 hybridization state
  - 1 biaryl bond
  - 1 solubilizing group (mostly morpholine or piperazine, linked via an ethylene linker to an aryl ether or via a -CH2- linker to an aromatic ring), 1 amide, 1 aromatic fluoride or chloride



Rivaroxaban. Reg. 2008.
Oral Factor-Xa-
inhibitor (antikoagulant agent)



Linezolid. Reg. 2000.
Inhibits bacterial protein synthesis
(antibacterial agent)

Typical API synthesis

- 4-6 steps
- includes
  - an amide formation
  - a deprotection step (most likely of a N-Boc group)
  - a Pd-catalyzed C-C bond formation
- solubilizing group introduced by either a reductive amination or an O-alkylation step

Top 10 reactions for API synthesis by frequency

reaction	no. of reactions	% of all reactions
N-acylation to amide	1165	16.0
N-containing heterocycle formation	537	7.4
N-arylation with Ar-X	458	6.3
RCO_2H deprotection	395	5.4
N-subs with alkyl-X	390	5.3
reductive amination	386	5.3
N-Boc deprotection	357	4.9
Suzuki cross-coupling reaction	338	4.6
O-substitution	319	4.4
other NH deprotection	212	2.9
total	4557	62.4

Roughley & Jordan, The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. J Med Chem 2011, DOI: 10.1021/jm200187y

Atom efficiency (atom economy)

- the conversion efficiency of a chemical process in terms of all atoms involved (starting materials, reactants, products)
- $\mathrm{AE} = (\mathrm{Mr\ of\ product})/(\mathrm{Mr\ of\ all\ reactants})\ \mathrm{x}\ 100\%$
- important in terms of limitation of waste, including products of reagents, solvents etc
- high atom efficiency: e.g. catalytic hydrogenation
- low atom efficiency: e.g. Gabriel synthesis of amines

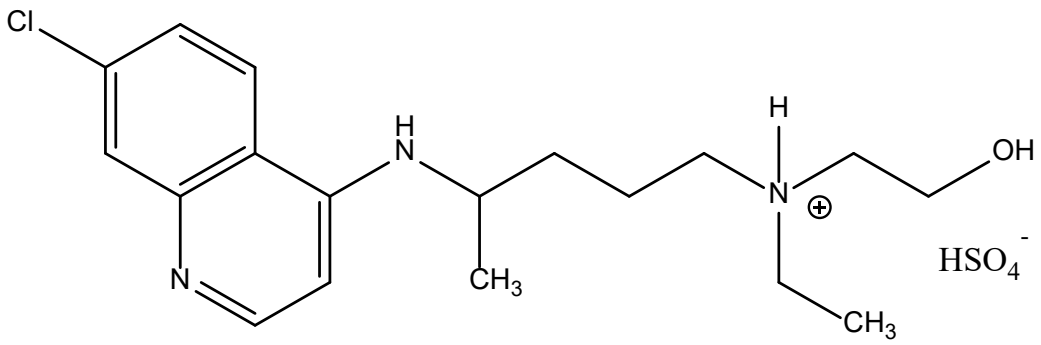
Waste

- by mass mainly solvents
- costly if hazardous (e.g. avoid chlorinated solvents)

Two example studies of API synthesis feasibility in Germany/Europe

How many steps away from synthesising an API in Germany?

Example: Hydroxychloroquine sulfate



- antimalarial
- antiinflammatory
- in vitro activity against Coronavirus; no therap. effect against COVID-19

Detail of the synthetic sequence

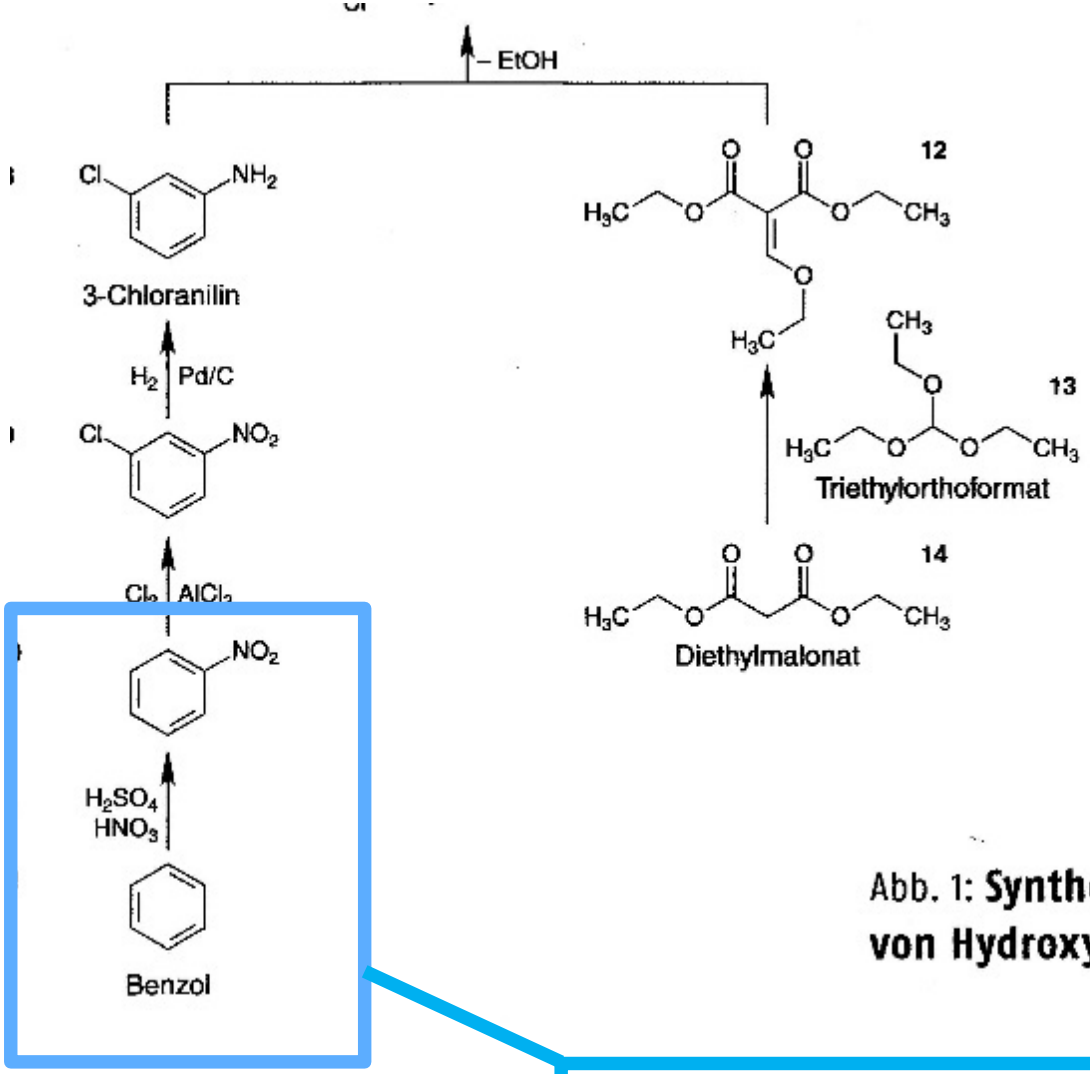


Abb. 1: **Synthesesequenz am Beispiel von Hydroxychloroquinsulfat**

available in Germany

Complete synthetic pathway

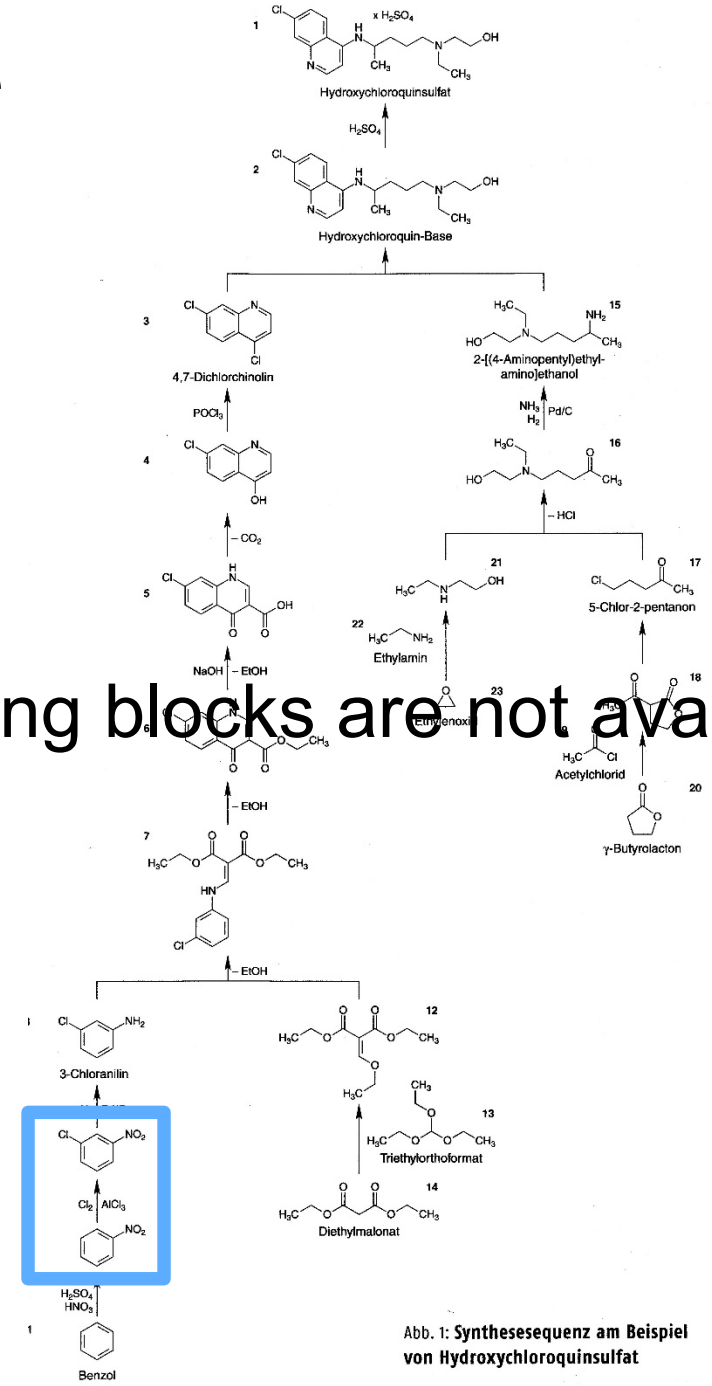
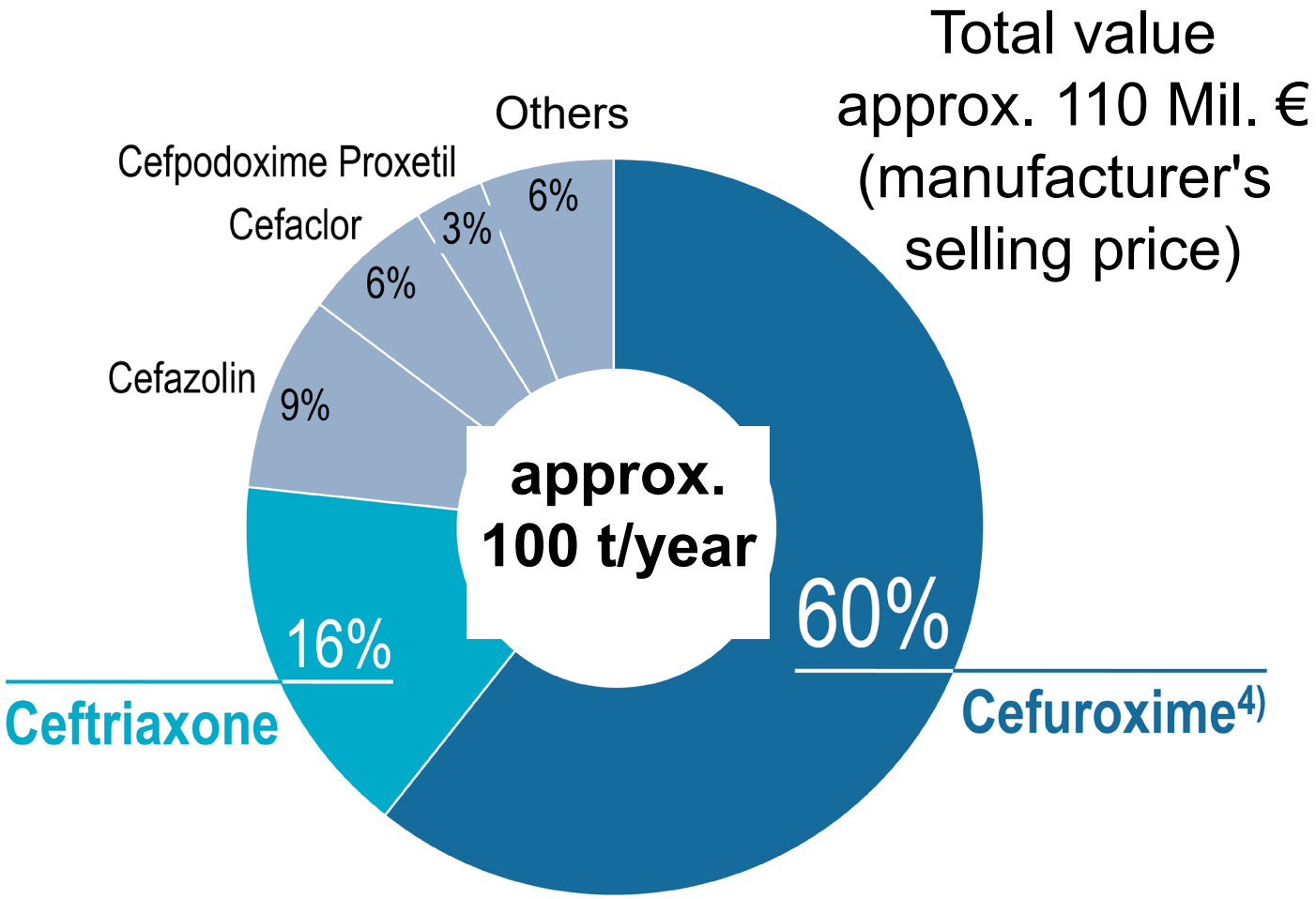


Abb. 1: **Synthesesequenz am Beispiel von Hydroxychloroquinsulfat**

Most building blocks are not available in Germany

Production of cephalosporins for humans in Germany? Analysis



https://www.progenerika.de/studien-roland-berger-antibiotikastudie-2018/

Fermentation → Intermediate → API

- Production of cephalosporin-C by fermentation:
  - grow fungi in cornsteep, fish and meat meal, saccharose, glucose and ammonium acetate
  - precipitate cephalosporin-C
- Enzymatic hydrolysis I:
  - oxidative desamination of the side chain by D-amino acid oxidase

  --> alpha-ketoadipyl-7-aminocaphalosporinic acid (ACA)
- Enzymatic hydrolysis II:
  - H_2O_2 + cephalosporin acylase --> oxidative decarboxylation to give glutaryl-7-ACA
  - + immobilised glutaryl-7-ACA acylase --> 7-ACA
- Synthesis of e.g. cefuroxim

Economical?

- Production of 500 t of cephalosporins (EU demand) → sales of approx. 125 Mil. €

→ negative business results if only production cost is detracted; more negative business results when distribution and admin costs are detracted

- Production of 100 t of cephalosporins to cover the German demand yields sales of only 25 Mil. €

→ not economical in Germany; main reasons: high operating and investment costs

- Why is it economical in Asia (Bangladesh, India, China)?
  - economies of scale (large production batches, worldwide sales)
  - relatively low cost of goods, personnel, admin, QC, logistics
  - capital investments in production plants are lower or amortised

Bwana asipoijenga nyumba Waijengao wafanya kazi bure. Zaburi 127:1
Unless the Lord builds the house, those who build it labour in vain. Psalm 127:1

Status quo in Africa

- K. Chibale et al. Drug Discovery in Africa 2012, p. 9:
  - "37 countries have some pharmaceutical production, and only South Africa has limited primary production of active pharmaceutical ingredient (API) and intermediates. ...
  - With the partial exception of South Africa, production in sub-Saharan Africa is generally limited to final formulations, characterized by non-complex, high-volume essential products, encompassing basic analgesics, simple antibiotics, anti-malarial drugs, and vitamins."

Ex Africa semper aliquid novi?

- API production plants are getting fewer worldwide
- Modern API production: improved process chemistry (costs reduction 5-35%), continuous manufacturing (cost reduction 10-25%), modular plant design (faster construction of the plants)

➢ adopt cutting-edge technologies without having to replace existing technologies and protocols

➢ Identify APIs that are accessible, serve a particular need and are of low interest to the "big players" in API production

➢ Tentative suggestion: go for antiinfective APIs that are produced by 1-2 companies only worldwide at present