Study on the security of antibiotics supply: Pathways towards a production of antibiotic APIs in Germany and the EU

Study report

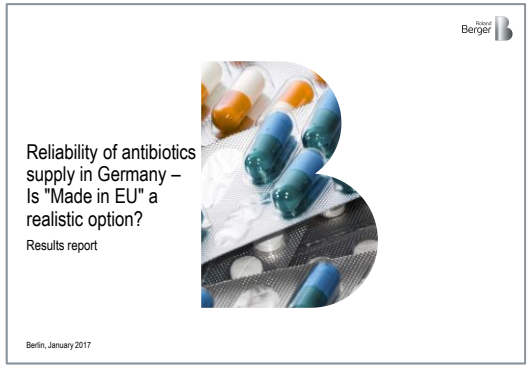
Berlin, November 2018

Based on the previous study in 2016, approaches to relocate/rebuild local antibiotic API[1)] production are investigated

Background and methodology of the current study (June - November 2018)

Background

- Due to the low price level of generic antibiotics, local production in Germany is no longer economical
- Supply bottlenecks in the German market due to a concentration of manufacturing capacity in low-wage countries
- Increase of supply risk due to dependence on foreign production
- Increasing discussion on the return of production capacity to Germany or the EU as a lever for securing supply



Study on the analysis of a relocation of antibiotic API production to Germany

1. Overview on **backgrounds** regarding **the need** to **rebuild local production capacity**
2. Description of the **production process to be repatriated** and the **required capacities**
3. Calculation of different scenarios and subsequent analysis of the **economic viability** regarding the relocation of a **local antibiotic API production**
4. Evaluation of **possible operator models** for the repatriation of antibiotic API production

1) Active pharmaceutical ingredient

Source: Roland Berger

The 2016 study found that local production capacity can reduce dependency and increase the security of supply

Results of the 2016 study: Overview of the current situation and expected effects

Situation

- **High import ratio of intermediates** and **APIs** for antibiotics that are processed in Germany
- **Dependence on foreign intermediate and API producers** which are mainly located in non-EU low-cost countries
- **Endangerment** of the **supply** with antibiotics and **occurrence of supply shortages**

Proposal

Entry into discussions with stakeholders regarding a partial relocation/reconstruction of the intermediate and API production for (generic) antibiotics to/in Germany and the EU

Expected effects

- **Reduction** of **(political) dependence** on imports from non-EU countries
- Assurance of **continuous supply** with **high-quality antibiotics** in Germany
- **Preservation/Extension** of production capacities and knowledge which are relevant for the **production of "next-generation" antibiotics**
- **Additional** positive **effects** possible
  - **Export of intermediates and APIs to EU neighbor states**, especially in the event of supply disruptions of non-EU producers
  - **Strengthening Germany as a business location** in the face of international competition
  - Generation of **additional value** for the **domestic economy** and **creation of jobs** through the operation of production facilities

Source: Antibiotics study 2016; Roland Berger

The production of antibiotic intermediates and APIs has been gradually relocated to non-EU countries

Relocation history: Relocation of antibiotic intermediate and API production

Systematic construction of production capacities in China

> **Subsidization** of **local production of intermediates and APIs** to ensure China's independence regarding antibiotics production during the 1980s
> Extensive **capacity building** for the production of **APIs** for **human and veterinary drugs**
> **Continuous efficiency improvements** and **further extension** of **production capacities**, even after satisfaction of local demand, leading to **excess capacities**
> Achievement of **economies of scale**

Increasing share of generic antibiotics after patent expirations in Germany

> **Rising costs of local** intermediates and APIs production due to increasingly challenging audits of comparatively outdated production plants and cost disadvantages
> **Reduction** of **(cost-intensive) local capacities for the production of APIs and intermediates** by originators after patents expirations
> Demand for **economically attractive capacities** for the production of intermediates and APIs
> **Expansion** of **production capacities** for intermediates and APIs **outside Germany** due to increasing cost pressures

Availability of low-cost production capacities in China

Demand for efficient production capacities for Germany

Shift of the production of intermediates and APIs for antibiotics to China and other low-cost countries outside the EU

Source: Expert interviews; Antibiotics study 2016; Roland Berger

I

Global and local factors maintain imports of intermediates and APIs from low-cost, non-EU-countries attractive

Current drivers: Relocation of intermediate and API production

Price pressure

> Low prices of (generic) antibiotics due to statutory health insurance **price setting mechanisms** as well as the **buying power** of hospital purchasing groups
> **Efficient production** of (generic) antibiotics thus **only possible** through **cost savings in the production**

Availability of capacities for the production of intermediates and APIs abroad

> Continuous **expansion and efficiency improvement of production capacities,** a.o., due to the globally growing demand for APIs[1)]
> Decline in the demand for veterinary antibiotics, thus **utilization of these capacities** for the production of **APIs for human antibiotics**
> Necessity to **reach a minimum production quantity**[2)] to cover the fixed costs and optimize the capacity utilization

Continued production of intermediates and APIs in low-cost, non-EU countries

Local factors

Demand fluctuations and peaks

> **Fluctuations in the demand** for (generic) antibiotics which can be **absorbed** more flexibly through the **externalization of production steps**

Global factors

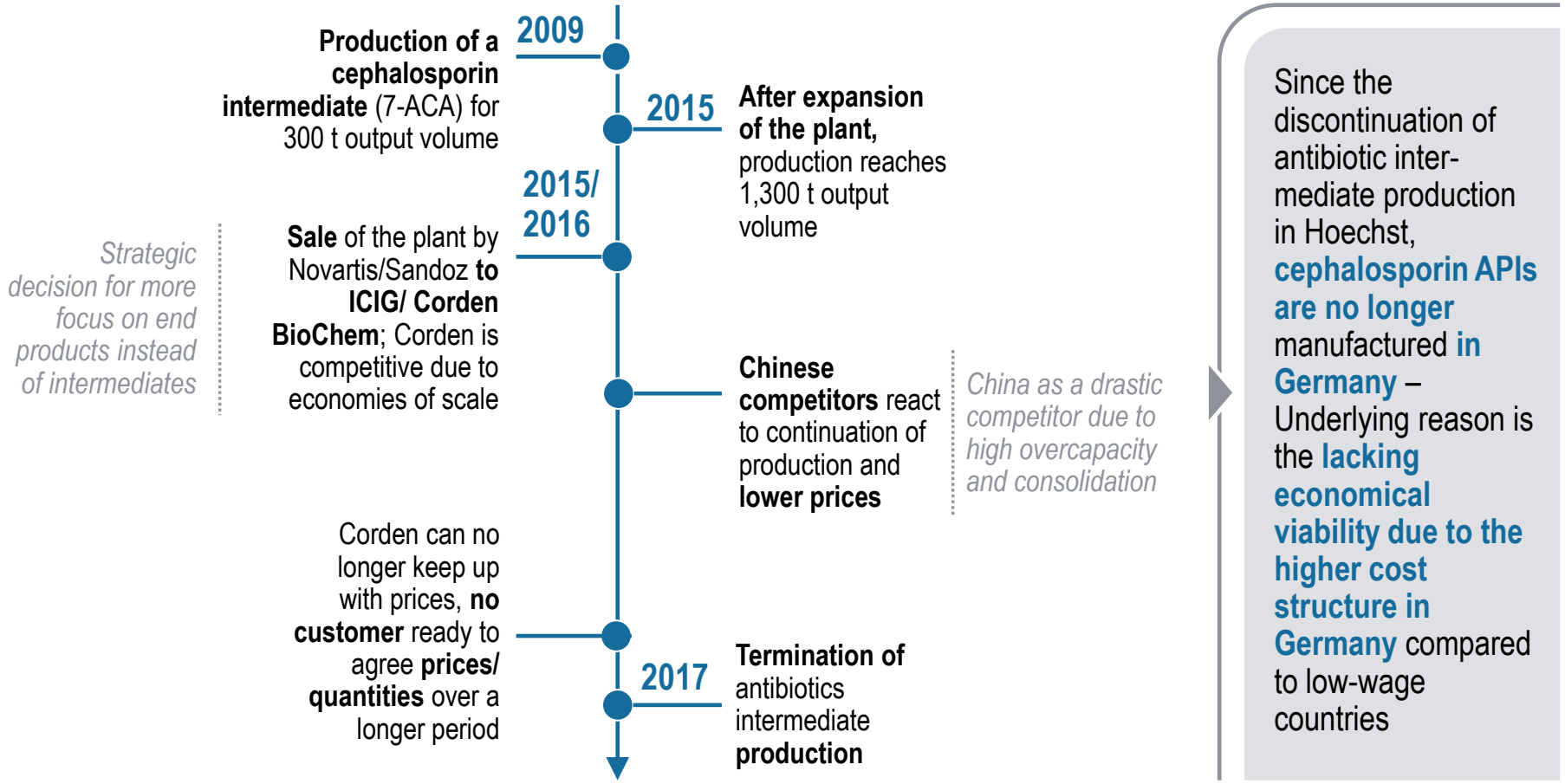
Cost advantage

> **Cost-efficient production** of **intermediates** and **APIs** due to
  – **Labor cost advantages**
  – **Less stringent production requirements** (environment, safety)
  – **Lower production costs** (especially for cooling and hence energy)
  – **Scaling effects** resulting from high production volumes

1) CAGR of around 10% between '12-'16 2) Long lasting fermentation processes which cannot be interrupted or resumed easily (continuous operation during 365 days/year)
Source: Statista; Expert interviews; Antibiotics study 2016; Roland Berger

This led, e.g., to the cessation of cephalosporin intermediate production in Hoechst – Production no longer economical

Example: 7-ACA production site Hoechst



Source: Expert interviews; Roland Berger

I

As a consequence, penicillins are mainly produced in low-wage countries – Germany is "on a drip"

Dependence on intermediate/API suppliers – Example of amoxicillin-antibiotics

Fermentation of 6-APA

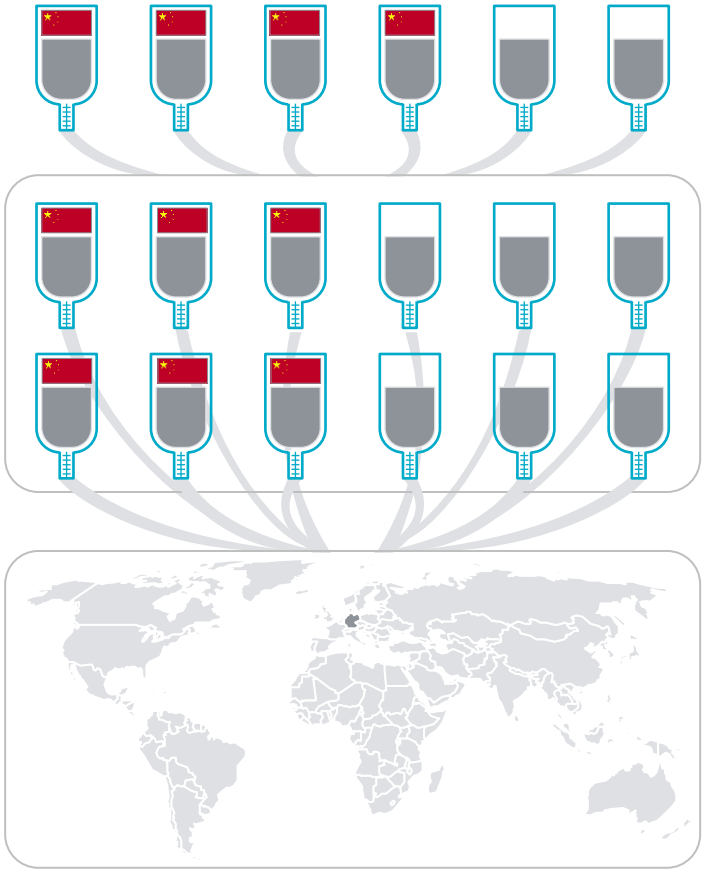
> **Four** relevant production sites **in China** + **two** relevant production sites **outside of China**[1)]

Chemical synthesis of amoxicillin trihydrates[2)]

> **Six** relevant production sites **in China** + **six** relevant production sites **outside of China**[1)]

Generation of antibiotics containing amoxicillin

> **Production of all antibiotics** containing amoxicillin in Germany/globally **dependent on intermediates and APIs supplied from these production sites** which are mostly located in Asia



6-APA is the **key molecule** for the production of antibiotics in the group of **penicillins**

Amoxicillin is one of the most **important APIs in the group of penicillins**

Drugs containing amoxicillin belong to the **most commonly used antibiotics** in Germany according to the DDD

1) Operated by global pharmaceutical companies 2) Mainly based on 6-APA
Source: Quintiles; IMS; Insight Health; Expert interviews; Antibiotics study 2016; Roland Berger

A relocation/reconstruction of antibiotic API manufacturing capacities is highly desired by numerous stakeholders

Voices from the 2016 study on the local intermediate and API production

Physicians

"In the event of a supply shortage of a given antibiotic, broad-spectrum-antibiotics are usually employed. As a consequence, the likelihood of the development of antibiotics resistances increases significantly",
German Society for Infectiology

The supply of specialty antibiotics should always be ensured

Pharmacists

"Politicians have to decide whether they continue to focus on cost efficiencies or whether they secure the supply of high-quality medicines by creating investment incentives that allow the industry to resume local production",
Pharmacist's chamber of Baden-Wuerttemberg

Politicians should guarantee the supply of medicines by incentivizing domestic production

Government

"It is desirable that producers, at least partially and with a focus on key intermediates, relocate their production to Europe",
BfArM

Essential intermediates and APIs should be produced in Germany again to guarantee the supply of medicines in the long-term

Producers

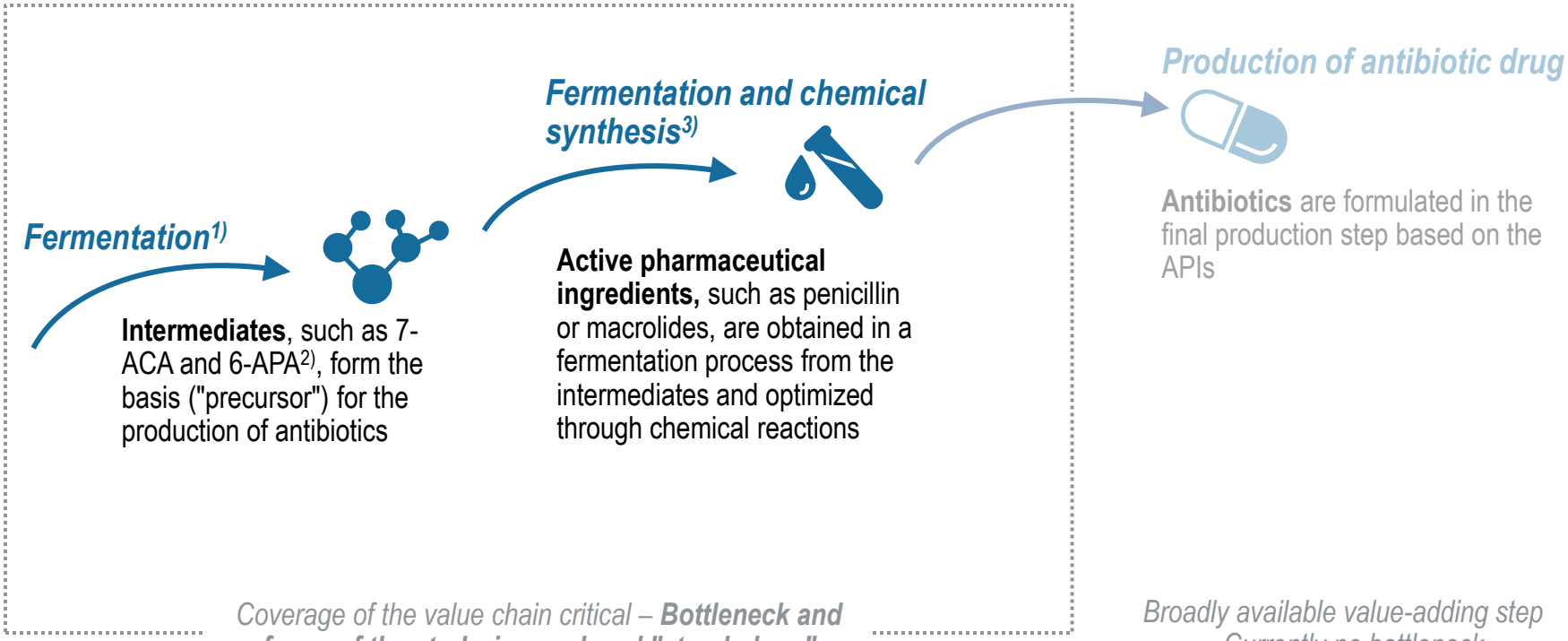
"Increasing cost pressure forces manufacturers to exhaust all possibilities to increase efficiency. This leads to a manufacturer concentration and shift of production towards locations outside the EU where production is economically viable",
Producer of generic antibiotics

The current price structure of the drug market does not allow for cost-efficient production within Germany/the EU

Source: Antibiotics study 2016; Roland Berger

Local intermediate production is economically not viable – Hardly any production facilities for fermentation or synthesis remaining in Europe

Overview of the necessary steps in industrial antibiotic production

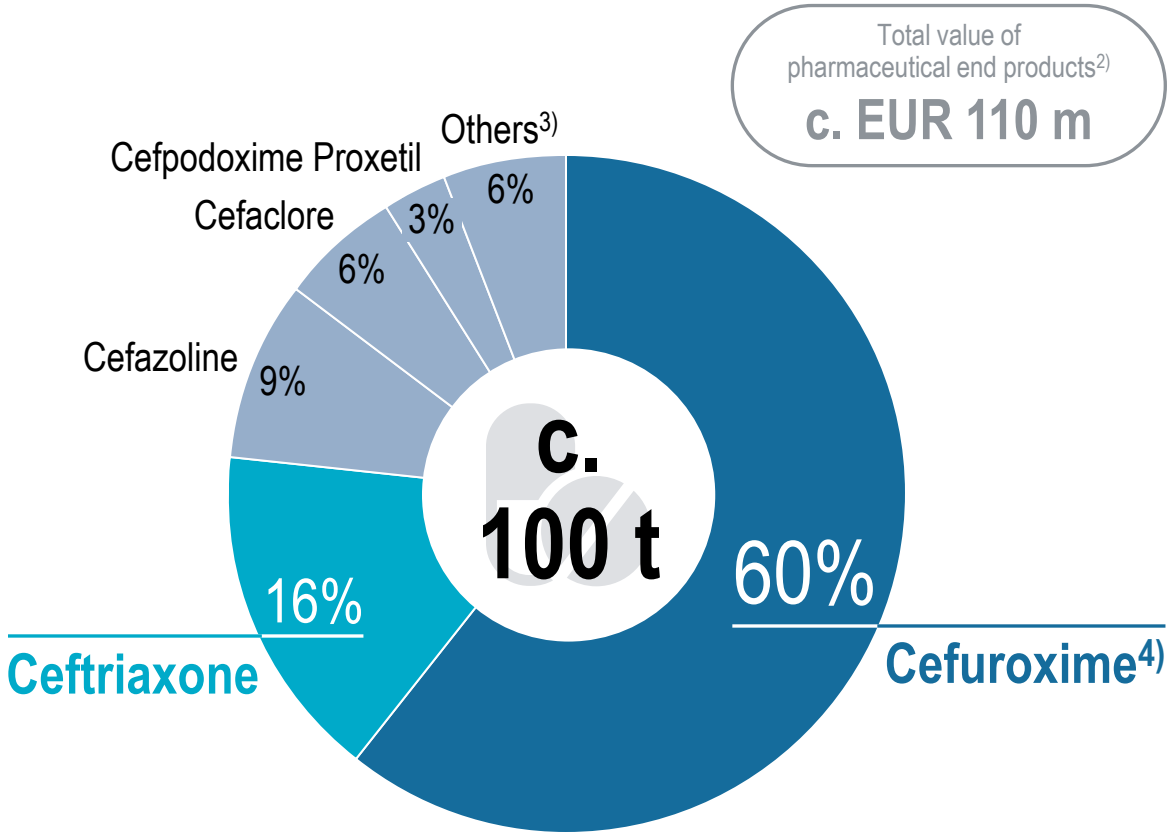


1) Production of raw material 2) "7-aminocephalosporanic acid" and "6-aminopenicillanic acid", which serve as the basis for semi-synthetic cephalosporin or penicillin
3) Production of API
Source: Roland Berger

Currently, no local production of cephalosporin intermediates – Exemplary analysis of an according relocation of production capacity

Generic cephalosporin consumption in Germany[1], 2017 in tons

- Since the **production stop in Hoechst** in 2017, **no generic cephalosporins including their precursors** have been **manufactured** in Germany
- In parallel to (amino)penicillins, **cephalosporins are widely used** and accordingly **represent a highly important group of antibiotics**
- To **ensure supply for cephalosporin consumption in the German market**, c. **100 t of the API** need to **be produced** annually



1) Human medicine only 2) At ex-factory price 3) Includes ceftazidime, cefotaxime, cefixime, cefadroxil, cefepime and cefalexin 4) Both cefuroxime and cefuroxime axetil

Source: IQVIA; Roland Berger

The analysis focuses on the manufacturing steps ranging from the fermentation of the intermediate to the final API synthesis

Contemporary manufacturing process of 7-ACA including cefuroxime synthesis

d Generation of 7-ACA

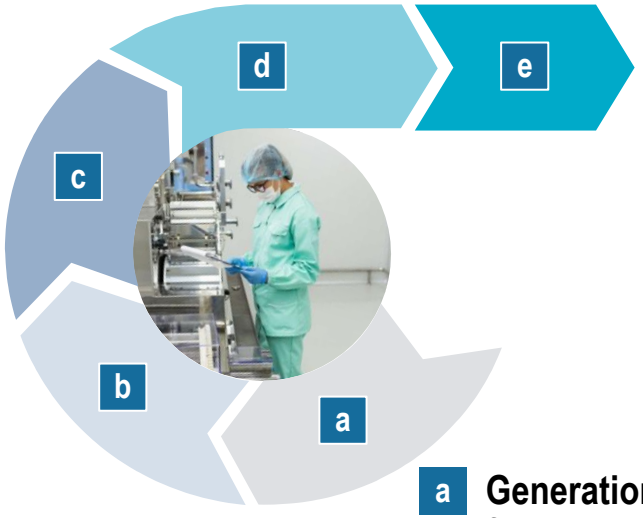
> The precipitated 7-ACA is filtered, washed with methanol, and water and is subsequently removed

e Synthesis to cefuroxime

> 7-Glutaryl-ACA is obtained by introducing a protective group on the free amine in the 7' position
> Subsequent carbamate ester formation at the 3'OH using chlorosulfonylic isocyanate
> Removal of the protective group at the 7' position by enzymatic hydrolysis of the amide bond (glutarylic acylase)
> Recovery of the final product by acylation of the free amine with 2-furanylic (sin-methoxyimino)acetic acid chloride

c Enzymatic hydrolysis II: Cephalosporin acylase

> By consumption of the formed H_2O_2 and irreversible oxidative decarboxylation Glutarylic-7-ACA is formed
> By using an immobilized glutarylic-7-ACA-acylase, the intermediate 7-ACA is obtained



b Enzymatic hydrolysis I: D-amino acid oxidase

> Oxidative deamination of the cephalosporin C side chain in aqueous solution by D-amino acid oxidase enzyme
> Aerobic production of α-Keteoadipylic-7 ACA, NH_3 and H_2O_2

a Generation of cephalosporin C by fermentation

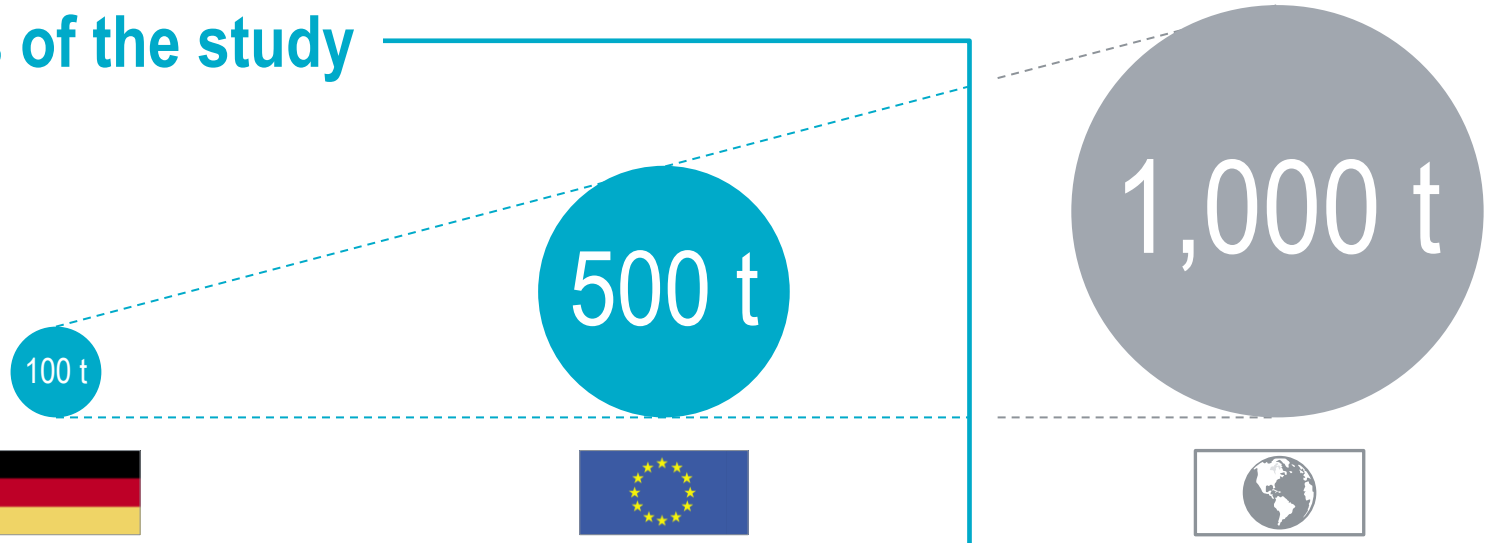
> The filamentous fungus *Acremonium chrysogenum* is combined with cornsteep solution, fish meal, meat meal, sucrose, glucose and ammonium acetate
> Cephalosporin C is produced with the aid of inorganic salts

Source: Desk Research (Biotechnology understandable, Technical Chemistry, Essentials of Industrial Microbiology, Industrial Microbiology); Expert interviews; Roland Berger

Investigation of three production scenarios for cephalosporin intermediates – Focus on the German and EU scenarios

Production of supply demand for Germany, EU and beyond: Three different scenarios

Focus of the study



Low scenario

Annual production volume of 100 t, roughly corresponding to the local demand in Germany

Medium scenario

Annual production volume of 500 t, covering most of the European demand

High scenario

Annual production quantity of 1,000 t, which would be desirable from a production-efficiency point of view as a minimum quantity (economies of scale) – Significantly exceeding the demanded supply in Germany or the EU

Source: Expert interviews; Roland Berger

German antibiotic consumption with c. 20% of Europe's top 5 markets consumption – 500 t calculated for European market coverage

Antibiotics consumption in Europe's top 5 markets as a basis for calculation

Antibiotics consumption in Europe's top 5 markets
(all active substances)

Country	Absolute [DDD m]	Percentage [%]
	c. 740	29%
	c. 535	21%
	c. 448	18%
	c. 425	17%
	c. 371	15%
Total	***c. 2.519***	***100%***

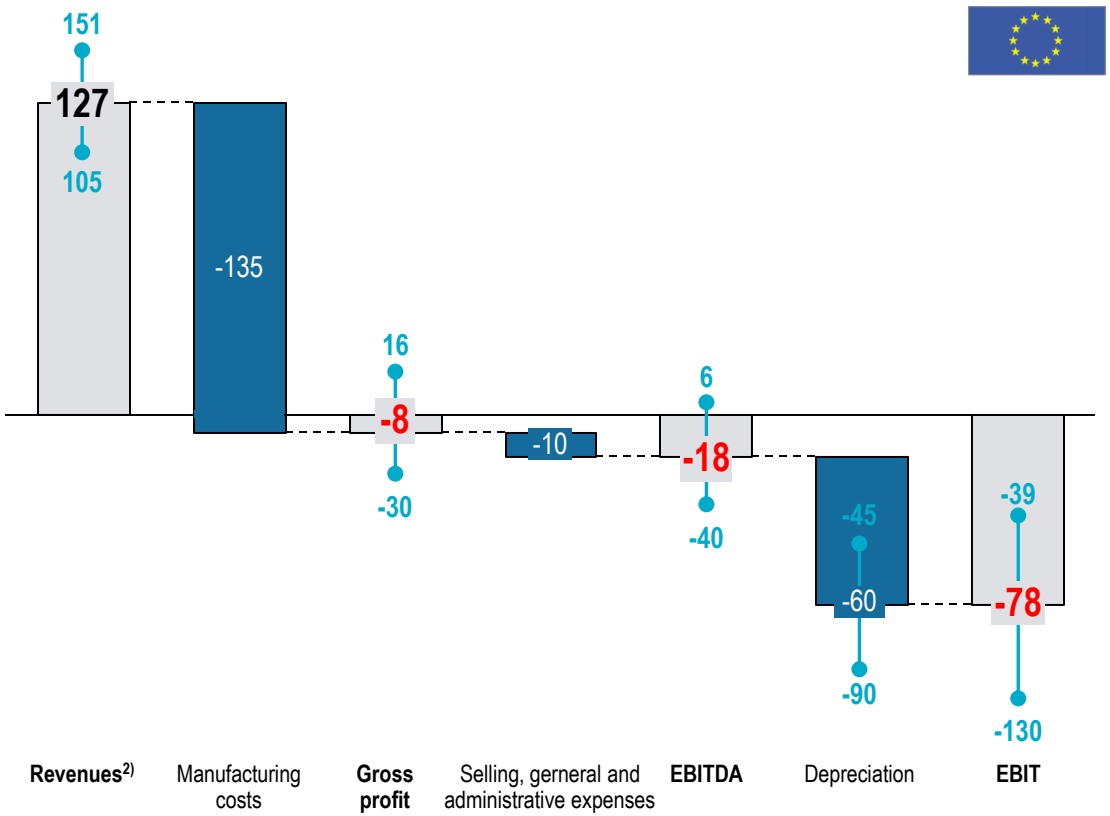
Basis of calculation

- **German antibiotic consumption** accounts for almost **20% of consumption in Europe's top 5 markets**
- The **German annual consumption** of **cephalosporins** is c. **100 t**
  - Accordingly, the **cephalosporin API production** of **500 t would cover** the **European market** to a large extent

Source: OECD; Roland Berger

The local production of antibiotic APIs for the European market is economically not viable – EBIT of c. EUR -78 m on average

Approximated P&L[1] of local API production for European market, 500 t [EUR m]



Comment

- Production of 500 t of cephalosporin APIs in Germany for the European market would generate revenues of EUR 105 to 151 m
- Operative result after deduction of manufacturing costs already negative on average
  - Selling, general and administrative expenses and depreciation with a further negative effect on the operative result

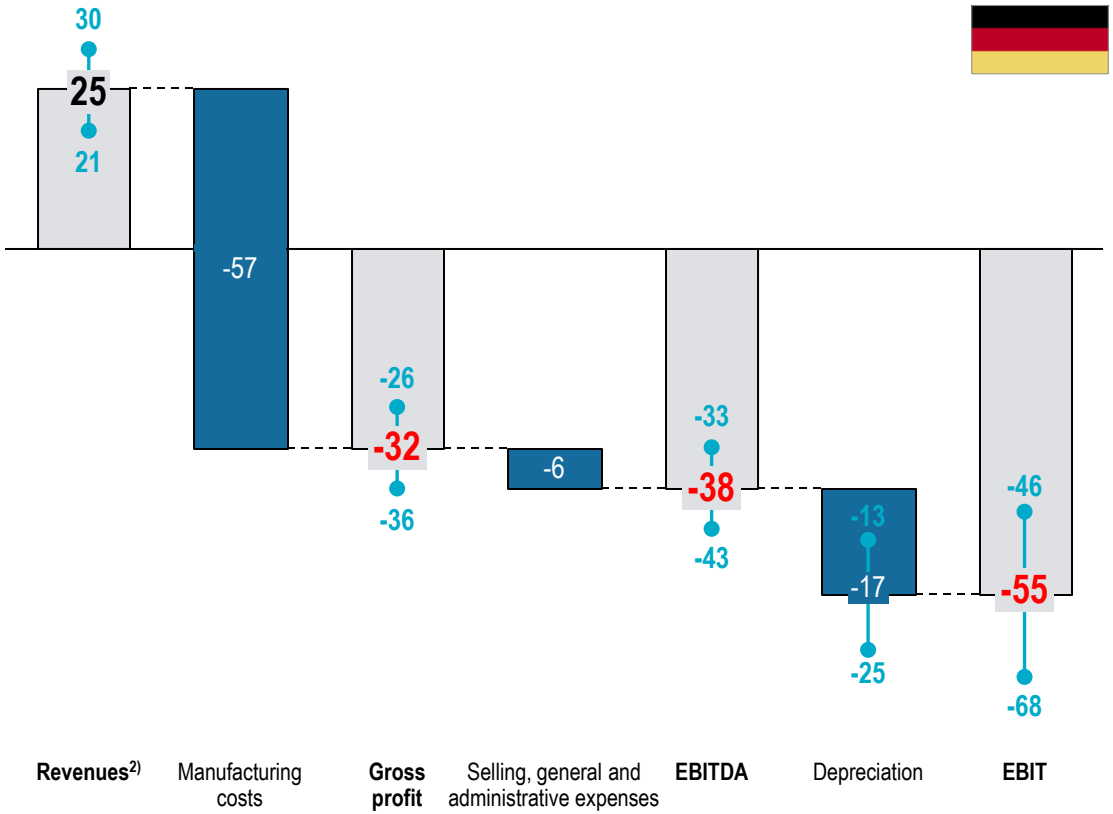
Margin depends on modeled price and cost development for APIs/finished products as well as depreciation periods

1) Profit and loss account 2) Revenues at ex-factory price

Source: Expert interviews; Roland Berger

Also, the API production for the German market is not economical – Total deficit lower than deficit of production for Europe

Approximated P&L[1] of local API production for German market, 100 t [EUR m]



Comment

> The production of 100 t of cephalosporin APIs to cover domestic consumption in Germany expected to generate revenues of c. EUR 21 to 30 m

> High manufacturing costs (mainly driven by low economies of scale) and the necessity of significant investments with associated depreciation lead to a negative operative result

Negative EBIT in absolute terms **lower than** production **for European market**

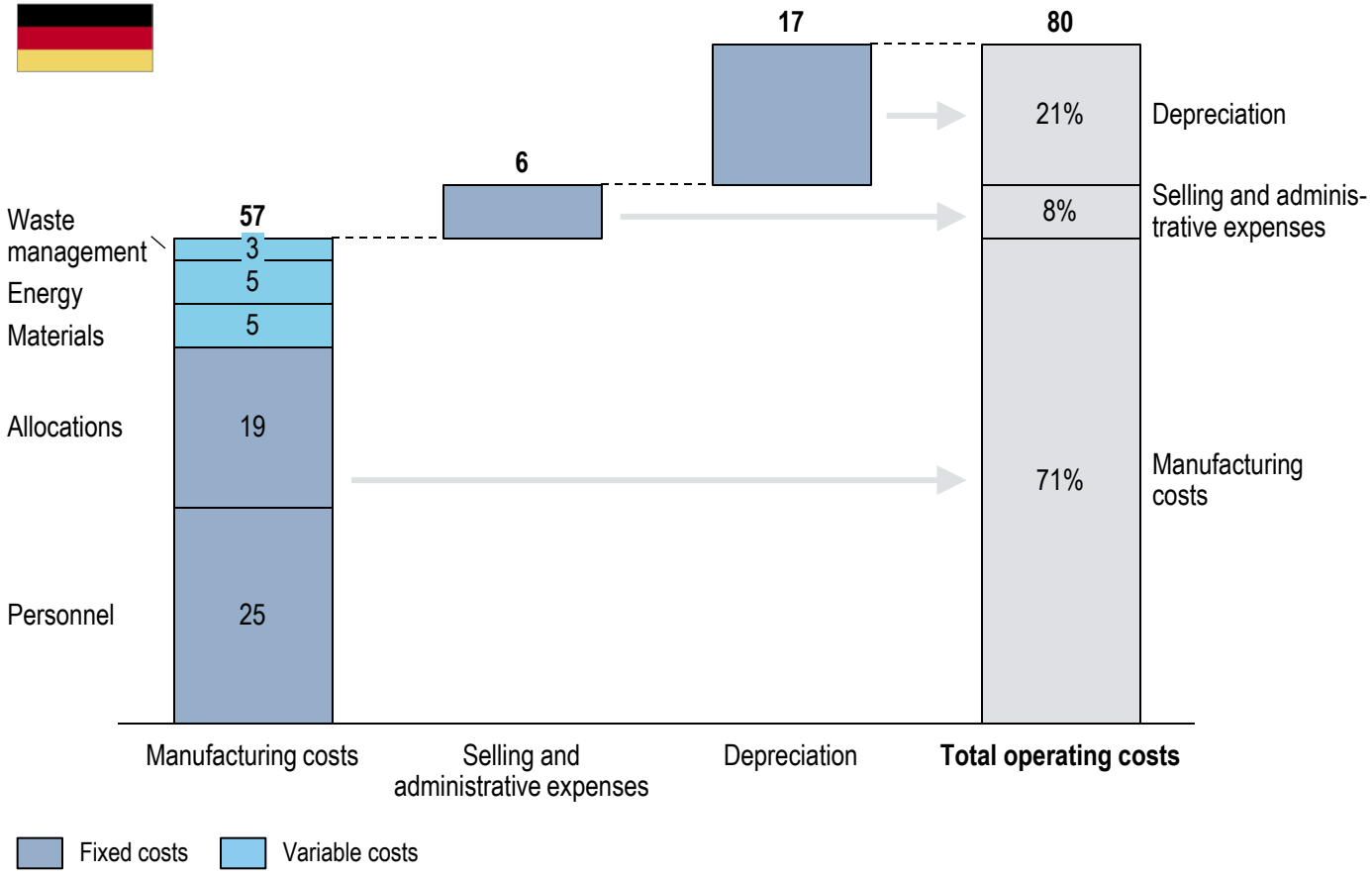
Margin depends on modeled price and cost development for APIs/finished products as well as depreciation periods

1) Profit and loss account 2) Revenues at ex-factory price

Source: Expert interviews; Roland Berger

The main reasons for the sub-economic production in Germany/ the EU are high operating costs and significant investments

Operating costs of local API production for the German market, 100 t [EUR m]



Why are the costs so high?

> Compared to the competition in Asia, manufacturing costs in Germany are significantly higher – Reasons are
  - Low economies of scale (production only for Germany)
  - High costs for personnel and allocations (e.g. quality control, logistics, production management)
> Moreover, investments and thus depreciation are significantly higher in Germany than in Asia – Higher personnel costs necessary for plant construction

Source: Expert interviews; Roland Berger

The production of antibiotic APIs in Germany is economically not viable in all three scenarios assessed

Reasons for and results of the sub-economic local antibiotics production

Investments	Comparatively high costs in plant construction
Personnel costs	German wages comparatively high, resulting in higher operating and administrative costs
Standards	High safety and environmental standards, thus comparatively costly production
Revenue potential	Fluctuations in demand for antibiotics and prices for APIs increase challenges to maintain operations according to plan

EBIT result of pro-duction scenarios[1)]

Low scenario (100 t)
EUR -55 m

Medium scenario (500 t)
EUR -78 m

High scenario (1,000 t)
EUR -55 m

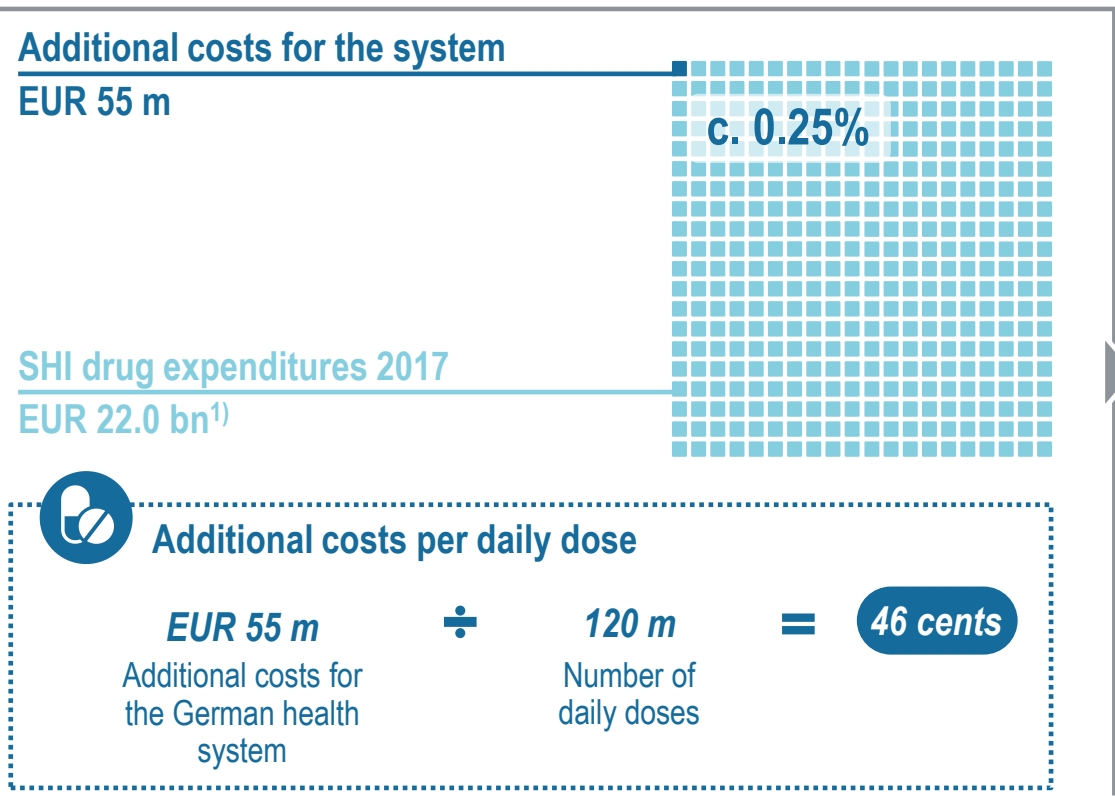
1) Average values of the profit and loss account

Source: Expert interviews; Roland Berger

To compensate for the negative EBIT of the production for Germany, the health system would need to bear EUR 55 m of additional costs

Theoretical additional costs for a local API production for the German market

Additional costs of a local production
(using the example of generic cephalosporins)



- The **additional costs** relate exclusively to the **local production of cephalosporins**, the second most prescribed group of all antibiotics (after amino-penicillins)
- The share of the total SHI expenditure on pharmaceuticals incurred by the pharmaceutical industry (including raw materials) amounts to c. EUR 22.0 bn in 2017 in Germany
- The **total additional costs of EUR 55 m** are equivalent to
  - additional costs per **daily drug dose** of **46 cents**
  - **c. 0.25% of SHI drug expenditures**[1)] in 2017

1) Proportion of SHI drug expenditure incurred by the pharmaceutical industry (incl. raw materials) at ex-factory prices – PHI not included

Source: ABDA statistics; Roland Berger

In order to increase the security of supply in Germany via local production, governmental support appears necessary

Range of options for governmental support

In order to make the local production of cephalosporin APIs attractive for the private sector, pathways needed to offset the negative EBIT by government intervention

Options of governmental support

1 ***Governmental intervention to market mechanisms to increase end prices***

> Increased revenues by ensuring higher end prices in the market, e.g. via intervention in the tender market

2 ***Governmental subsidy for production costs***

> Governmental subsidies for the fixed and/or variable costs incurred during production, e.g. personnel and energy costs

Investment subsidy to reduce the amount of depreciation

> Governmental subsidy for the construction of production facilities and/or the purchase of land

3 ***Governmental remuneration for capacity provision to minimize supply risk***

> Governmental payments for maintaining production capacity of generic antibiotics to ensure security of supply

Source: Roland Berger

Advantages and disadvantages of the identified options for governmental support

Assessment of governmental support options

1 Price regulation via intervention to the tender market

Conditional increase of end prices in the tender market for products, based on locally produced APIs

Assessment

- ✚ No direct additional costs or administrative burdens for the government
- ▬ Increased costs for the health care system due to higher end prices for APIs produced in the EU

2 Price regulation via subsidies to the operations or to the investment

Governmental subsidy to render the total cost of local production competitive

- ✚ Possibility of targeted promotion of individual locations to increase the overall economic return
- ✚ Security for operators against regulatory/political fluctuations
- ▬ Relatively high one-off costs for the government to initialize operations

3 Protection against supply risks

Governmental payments for the provision of production capacity as risk protection against supply bottlenecks

- ✚ Government guarantees security of supply by keeping production capacities available – Direct return for public payments
- ✚ Tendering the risk protection leads to the highest possible efficiency, i.e. the lowest possible cost for the system
- ▬ Required commitment to cover costs by a governmental department (e.g. Federal Ministry of Finance, Federal Ministry of Health, Federal Ministry for Economic Affairs and Energy)

✚ Advantages ▬ Disadvantages

Source: Expert interviews; Roland Berger

For all options shown, possibilities for implementation exist – Cross-stakeholder coordination necessary

Implementation possibilities of governmental support options

1 Price regulation via intervention to the tender market

Conditional increase of end prices in the tender market for products, based on locally produced APIs

Implementation possibilities

> **Amendment** of existing national **legislation** for the **tendering of antibiotics** with regard to **"Made in EU"**
> Statutory preferential treatment of European production as a contribution to increasing the security of supply in Germany

2 Price regulation via subsidies to the operations or to the investment

Governmental subsidy to render the total cost of local production competitive

> **Investment subsidy** for a local site for the production of APIs with the effect of reducing depreciation to improve EBIT
> Contribution to the security of supply and promotion of the overall economic return

3 Protection against supply risks

Governmental payments for the provision of production capacity as risk protection against supply bottlenecks

> (EU-wide) **tender** for the **provision of production capacities** as a means of risk protection
> Contractually secured supply capability for longer periods by granting a regular basic charge

In principle, **all operator models** can be **implemented and combined** – **Collective initiative** and **discussion** between the affected **stakeholder groups** (e.g. industry, inpatient/outpatient care providers, politicians, health insurance funds) at national or European level necessary for **agreement on a solution model**

Source: Roland Berger

Reconstruction of production capacities with the help of governmental support aspired to achieve a sustainable reduction of dependency

Proposal and expected effects on the security of supply for (generic) antibiotics

Situation

- **Dependence on foreign antibiotic intermediate and API producers**, predominantly from non-EU low-cost countries, e.g. China
- **Production in Germany not economically viable** due to competition from low-cost countries at current price levels
- Repatriation of **local production** desirable to attain sustainable **long-term security of supply**

Proposal

- **Further joint investigation and implementation of possibilities** for the promotion of local antibiotic API production
- Three **possible operator models/ components**
  - **Price regulation** via intervention to the tender market
  - **Price regulation** via subsidies to the operations or to the investment
  - **Protection of supply risks** via governmental payments

Expected effects

- Ensuring of a continuous **supply of vital antibiotics** in Germany
- **Economic viability** for **operators of local API production** by permanently securing their commercial basis
- **Strengthening/maintaining know-how** for local antibiotics production and the domestic **production capabilities** (value creation/jobs)
- **Reduction** of **(political) dependency on** production in non-EU countries

Source: Roland Berger


Roland
Berger