

Reliability of antibiotics supply in Germany – Is "Made in EU" a realistic option?

Results report



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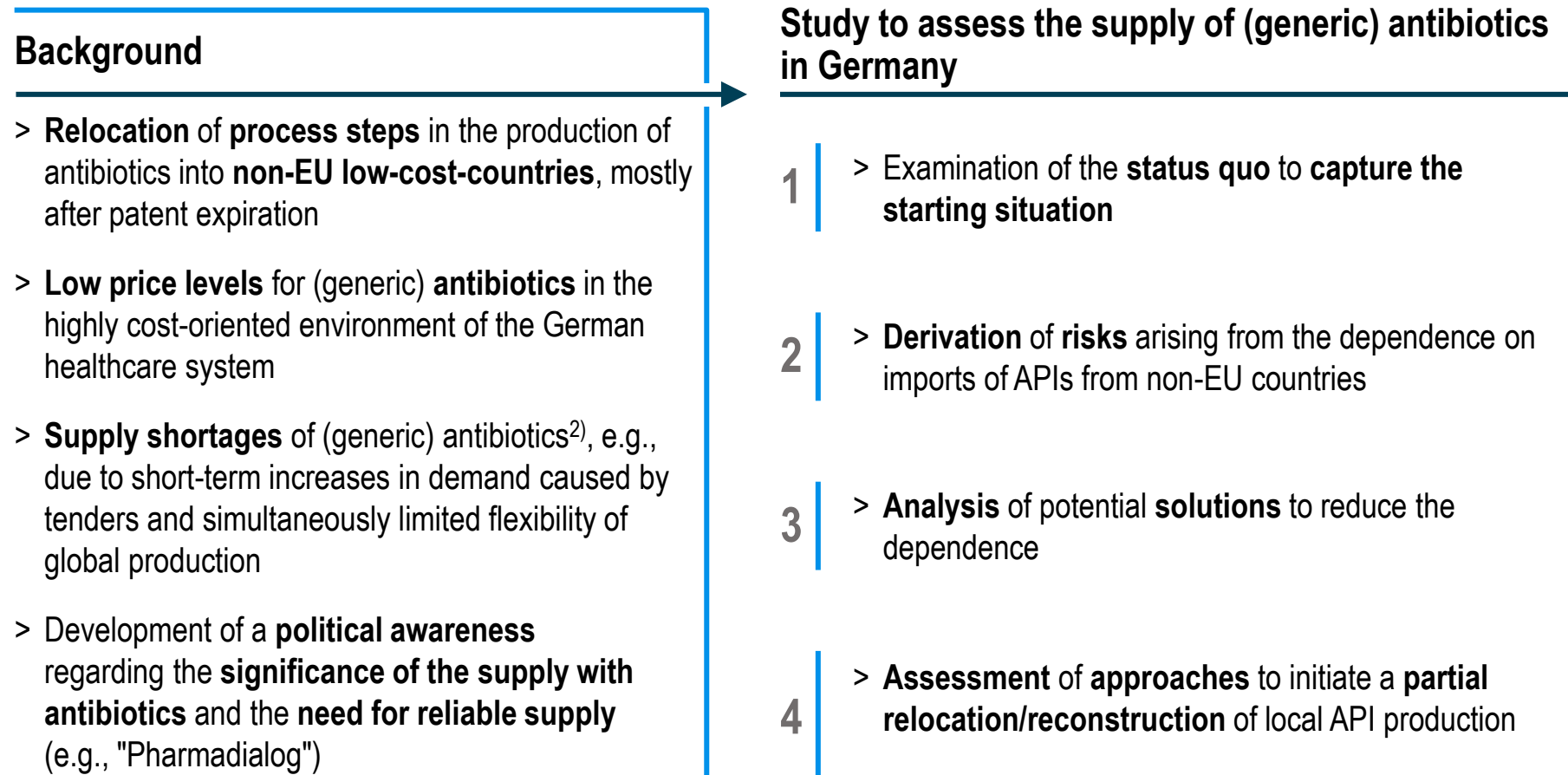
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A. Evolution of antibiotics production



This study examines the supply situation of generic antibiotics, given the dependence on API¹⁾ imports from non-EU countries

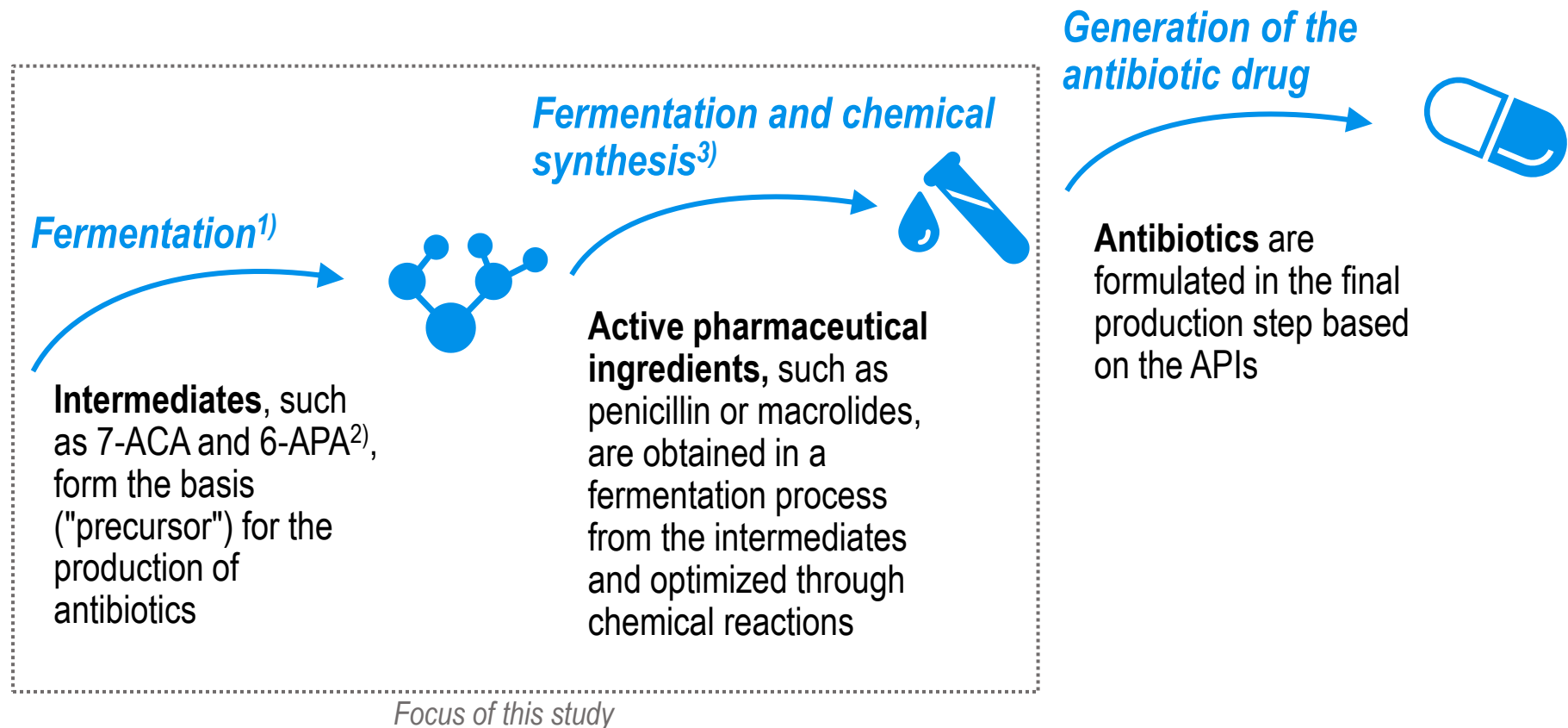
Background and methodology of the study (January – December 2016)



1) Active pharmaceutical ingredient 2) In the out-patient and in-patient sector
Source: Roland Berger

Antibiotics are produced in three fundamental steps – Generation of intermediates, transformation into APIs and drug formulation

Process of the 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: Expert interviews; Roland Berger

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

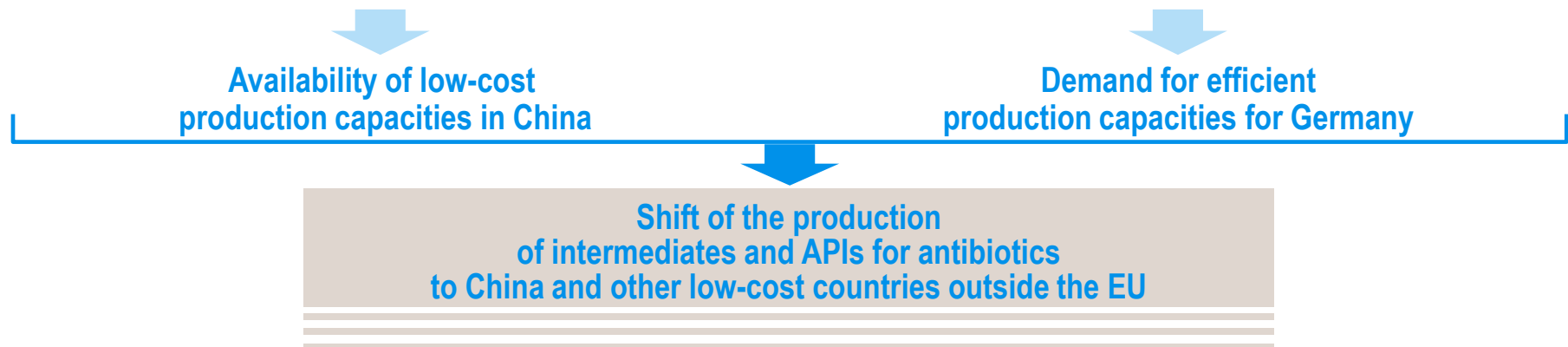
Relocation of intermediate and API production – Relocation history

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**

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 **Rising costs of local** intermediates and APIs production due to increasingly challenging audits of comparatively outdated production plants and cost disadvantages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



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

Relocation of intermediate and API production – Current drivers

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**

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**



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 APIs¹⁾
- > 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 to optimize the capacity utilization

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; Roland Berger

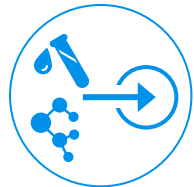
Thus > 80% of the processed intermediates and APIs are imported
 – Clear dependence on non-EU producers

Origin of intermediates and APIs processed in Germany



885 EUR m

Total value of APIs for antibiotics processed in Germany (for human- and veterinary drugs)¹⁾



> 80%

Share of intermediates and APIs that are processed in Germany but imported from non-EU countries¹⁾



China & India

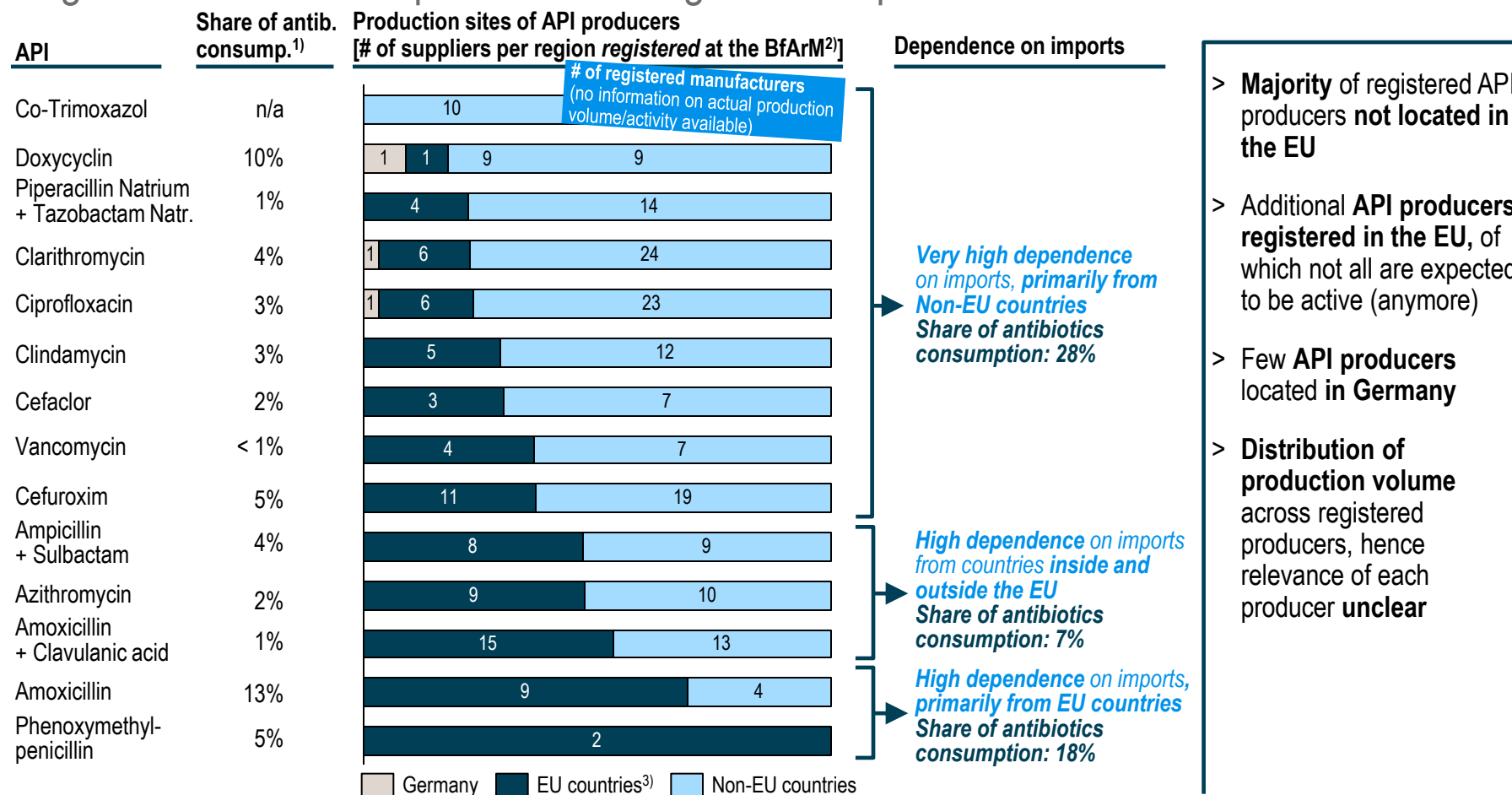
Main countries of origin of intermediates and APIs processed in Germany (and globally)²⁾

*German and global antibiotic manufacturers are **highly dependent on intermediate and API imports from non-EU-countries***

1) Own modelling for 2016; Generics and originators, out-patient and in-patient 2) Mongolia with increasing attractiveness due to lower energy costs for cooling

The majority of API producers is located abroad – Actual activity of locally registered suppliers unclear

Registered sites of API producers for high-consumption antibiotics

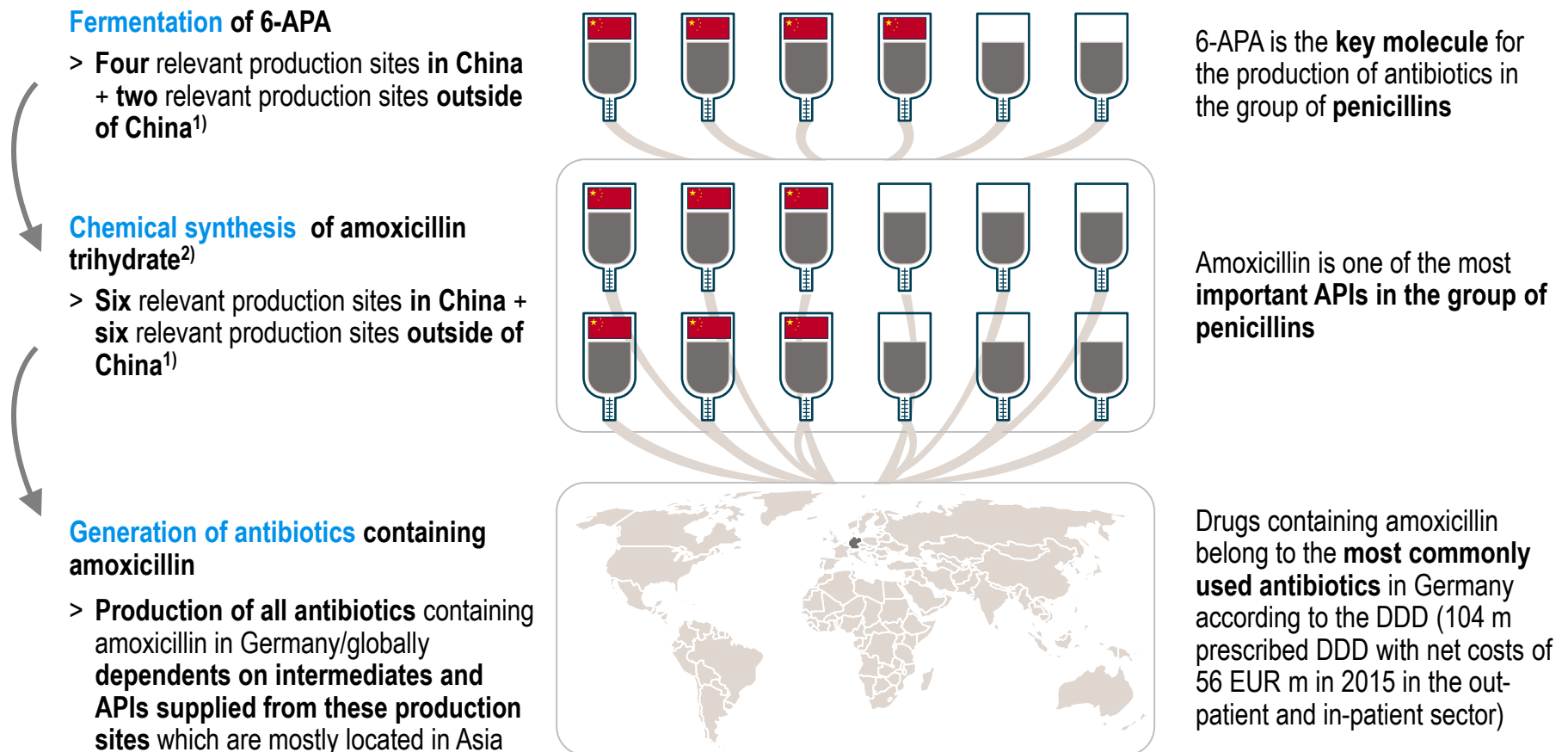


- > **Majority** of registered API producers **not located in the EU**
- > Additional **API producers registered in the EU**, of which not all are expected to be active (anymore)
- > Few **API producers located in Germany**
- > **Distribution of production volume** across registered producers, hence relevance of each producer **unclear**

1) % of antibiotics consumption in Germany according to total revenues, out-patient + in-patient, including ATC classes J01 (systemic) + S01 (ophthalm.) + D06 (dermat.) + other
 2) Federal Institute for Drugs and Medical devices 3) Excl. Germany Source: BfArM, IGES, expert interviews; Roland Berger 20161213_ProGenerika_Antibiotikastudie2016_ENG.pptx | 9

The global production of antibiotics containing amoxicillin depends on few intermediate and API manufacturers

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



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

B. Consequences of the dependence on non-EU producers



The dependence on imports of intermediates and APIs leads to supply shortages of (generic) antibiotics in Germany

Causes for supply shortages

1 Increasing concentration of foreign producers of intermediates and APIs, especially in China and India

- **Growing quality requirements** for local production plants, which cannot be fulfilled by all manufacturers
- **Expensive "multiple sourcing"**¹⁾ not feasible for German antibiotics producers due to cost pressure, thus lack of alternative suppliers in case of supply shortages
- Static production capacities of foreign intermediate and API producers; in case of a supply shortage commonly preferential coverage of local demand

*"Only few suppliers are available due to a high **market concentration**. Furthermore, we **cannot resort to back-up suppliers** in case of supply shortages **due to cost pressure**."*

Producer of generic antibiotics

2 Production deficiencies of foreign manufacturers

- **Operational problems** in the **production process** of intermediates and APIs, which may lead to delays in the supply
- **Quality deficiencies** of imported intermediates and APIs, thus uselessness of delivered products

*"**Deficiencies** occurring in production plants in **China or India** directly **affect antibiotic manufacturers in Germany**."*

Representative of pharmacists association

1) Antibiotic manufacturers engaging in multiple sourcing have at least two sources of supply for each intermediate/API required for the production of their drug

Numerous stakeholders in the healthcare landscape warn about supply shortages of (generic) antibiotics and their consequences...

Opinions on supply shortages of (generic) antibiotics

Physicians

„**Supply shortages** are **no isolated cases** anymore, they are gradually becoming an **systematic error.**“

Hospital physician

Systematic problems in the production process lead to unpredictable supply shortages of single products

Pharmacists

„The **concentration of a limited number of manufacturers** increases the **dependence on a few production sites** and thus the risk of a supply shortage.“

Member of the German Association of Pharmacists

The lack of alternative suppliers enhances the negative impact of individual supply shortages

Government

„The **limitation of production to a few production sites** which ensure the global supply with intermediates/APIs is problematic. Thus, production defaults might lead to **extensive supply shortages.**“

Federal Ministry of Health

The limited amount of producers for intermediates and APIs increases the danger of a supply shortage

Producers

„As the production process is **segmented into multiple steps**, shortages can occur more frequently based on **intermediates** being **supplied by Chinese manufacturers.**“

Producer of generic antibiotics

As a result of the complex production chain, a single production default can lead to significant restrictions and even to supply shortages

... and, hence, call for more local production capacities

Opinions on local production of intermediates and APIs

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 of 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

Could shortages in the supply of antibiotics be prevented through a partial relocation/reconstruction of local production facilities?

Partial relocation/reconstruction of local production as possible measure?

Core issue

- 1 | **High (political) dependence** on imports from non-EU countries in Germany
- 2 | **Risk of a supply shortage** in Germany in case of a disease outbreak, as exporting countries will first satisfy local demand for antibiotics before supplying foreign countries. **Availability of products with a significant time lag** after initiation of local production capacity construction
- 3 | Increasing **relevance** of the **production of antibiotics** and the **respective production knowledge** for the **development of new antibiotics** (e.g., increasing resistances)

Possible measure

**Partial relocation/
reconstruction of the
production of
intermediates and APIs
to/in Germany/the EU**

C. Validation of the
feasibility of a partial
relocation to
Germany/the EU



The relocation/reconstruction currently fails due to high production and investment costs and a low price level

Key hurdles for the relocation/reconstruction of local production

Comparatively high production costs in Germany/the EU

- > Extensive regulation of production requirements (Safety and environmental requirements)
- > High salary levels
- > Lack of relevant technologies

*"Due to the **high market concentration**, only few suppliers are available. Furthermore, we cannot resort to back-up suppliers during supply shortages due to the cost pressure which does not allow to maintain back-up suppliers."* Producer of generic antibiotics

Multiple production sites required

- > High investment costs per efficiently operating production site represent significant entry barriers, especially as multiple production sites per API are needed for safety reasons
- > Usually only production of a single API per production site possible to avoid cross-contamination

*"Shortages emerge due to **immense cost pressure** along the entire value chain."* Producer of generic antibiotics

Current low price level for antibiotics in Germany

- > Low willingness to pay for generics
- > World market price level below German production cost level

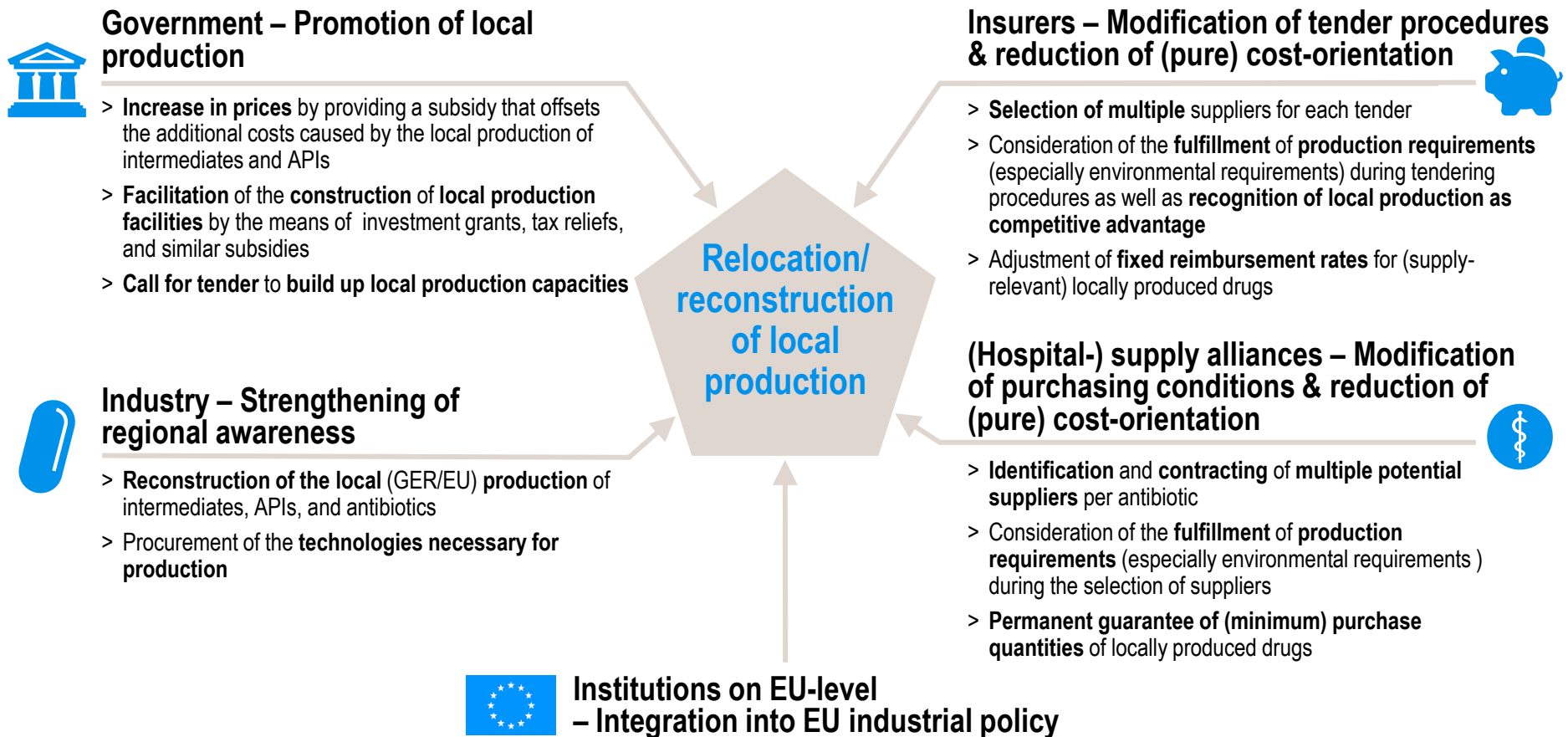
*"From a market point of view, **price levels are the main determinant of supply security** – there must always be enough margin for local investment."* Producer of generic antibiotics

"A relocation/reconstruction of local production is not possible without political measures that change the overall conditions ."

Producer of generic antibiotics

How can all stakeholders be involved to achieve a relocation of production and hence safeguard the continuous supply of antibiotics?

Starting points for the partial relocation/reconstruction of local production



D. Conclusion



A reconstruction of the local production decreases the dependence on non-EU imports and safeguards the continuous supply of antibiotics

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 antibiotics to/in Germany

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
 - **Reinforcement of Germany's position as production location** in comparison to international competition
 - Generation of **additional value** for the **domestic economy** and **creation of jobs** through the operation of production facilities

Roland
Berger

